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Multivariate modelling of the tablet manufacturing process with wet granulation for tablet optimization and in-process control

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Abstract

The process of tablet manufacturing with granulation is described as a two-step process. The first step comprises wet granulation of the powder mixture, and in the second step the granules are compressed into tablets. For the modelling of the pharmaceutical process of wet granulation and tableting, two models are constructed and compared. The first model relates the crushing strength (CS), disintegration time (DT) and ejection force (EF) of the tablets with process variables from both the wet granulation and tableting steps and the composition variables of the powder mixture. In addition to these predictor variables, the second model also uses physical properties of the intermediate granules to improve the predictive properties of the first model. Model 1 has to be used at the start of the process to find settings for the process variables and the composition of the tablet mixture that produce tablets with specific properties. Model 2 is used, in everyday production, for each new granulation batch. The granule properties may differ from batch to batch due to uncontrolled sources such as air humidity, temperature or other unknown features. With Model 2 these differences are taken into account, and the CS and DT are predicted better than with Model 1. The advantage of incorporating the measured granule properties in the second model is not only an improvement of the predictive power, but the second model offers also the possibility to use a control scheme for the second step of the process. This control scheme adjusts the variables of the tableting step to produce tablets that better meet the specifications. Because the granule properties are highly collinear and also dependent on the process variables of the first step, a partial least squares regression method has been used for the modelling. © 1997 Elsevier Science B.V.

Keywords: Multivariate process modelling; Wet granulation process; Granule properties; Tablet properties; In-process control

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1. Introduction

In the last 15 years, the process of wet granulation has been studied in a systematical way by experimental design and analysis of variance (ANOVA) (Holm et al., 1983, 1984a,b; and Jægerskou et al., 1984; Miyamoto et al., 1995) and by response surface methodology (RSM) (Lindberg et al., 1985a,b; Lindberg and Holmquist, 1987; Vojnovic et al., 1992, 1993; Wehrle et al., 1993). In most studies, the effect of the process variables on granule properties such as median granule diameter, percentage of fines, flow rate and porosity was investigated (Holm et al., 1983, 1984a,b; Jægerskou et al., 1984; Lindberg and Holmquist, 1987; Vojnovic et al., 1992, 1993). In some other papers, the effect of the process variables on the tablet properties was also investigated (Wehrle et al., 1993; Paschos et al., 1988; Westerhuis et al., 1996). Alderborn gave a list of granule properties that are important to tableting (Alderborn, 1988). Lindberg studied the influence of the granule properties combined with the process variables for the tableting step on tablet properties as crushing strength (CS), disintegration time (DT) and friability (Lindberg et al., 1985a,b). In this paper, physical granule properties are combined with the composition variables of the powder mixture and the process variables of both granulation and tableting steps to improve the modelling of the tablet properties. Therefore, the process of tablet manufacturing is described as a two-step process. In the first step, the powder mixture is wet granulated to improve the tableting properties of the mixture. Several process variables can be adjusted to change the physical properties of the granulations such as granulation time and amount of granulation liquid. The granulations are described in terms of particle size distribution, flowability parameters and poured and tapped volumes. In the second step the granules are compressed into tablets. Here other process variables such as compression force and moisture in the granules can be set to produce tablets with specific characteristics. The tablet characteristics include CS, DT and EF. Fig. 1 shows the two-step process of tablet manufacturing with a wet granulation step. The powder mixture is described in three phases, as a powder mixture P, as granules G and finally as a tablet T. The process variables PV1 and PV2 describe the transition from one phase to another.

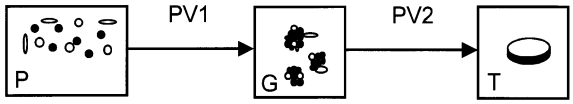

Fig. 1. The two-step process of tablet manufacturing by wet granulation.

Modelling of two-step or multi-step processes in pharmaceutical technology has not received much attention. Lundstedt and Thelin showed a multivariate strategy for optimizing a two-step process consisting of a synthesis and a purification step (Lundstedt and Thelin, 1995). Their strategy requires that the intermediate product contains all information from the starting materials and the process variables of the first step that is necessary for modelling and prediction of properties of the final product. In the tablet manufacturing process, however, only a few properties of the intermediate granules are measured, such as the particle size distribution and some flowability parameters. The granule properties do not have a strong relationship with the CS and DT of the tablets, and cannot be used solely for the modelling of the tablet properties.

The two-step process of wet granulation and tableting is modelled with two different models.

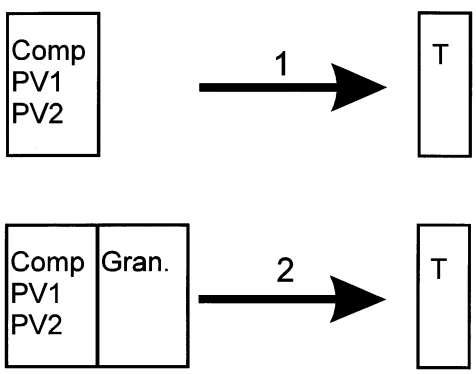

Fig. 2. Two models for the modelling of tablet properties. In Model 1, the composition variables and the process variables of both steps are used. The granule properties are added in Model 2.

Fig. 2 shows the two models for the process. The first model describes the relation between the combination of the composition of the powder mixture and process variables of both steps (PV1 and PV2) and the tablet properties. The first model can be used at the start of the process to find settings for the process variables and the composition of the tablet mixture that produce tablets with specific properties; e.g. when one wants to use less binder in the formulation, Model 1 can be used to find setting for the other process and composition variables to produce tablets that still meet the specifications. After the granulation step, physical properties of the granules, are added to the variables of Model 1. The granule properties do not represent all the information from the first step and cannot be used solely for the modelling of the tablet properties. They do however influence the physical tablet properties and can be used to improve the first model. Model 2 has to be used, in everyday production, for each new granulation batch. The granule properties may differ from batch to batch due to uncontrolled sources such as air humidity, temperature or other unknown features. With Model 2 these differences are taken into account, and tablet properties are predicted better than with Model 1. Model 2 offers the possibility to use a control scheme for each new batch of granulation, to adjust the process variables for the tableting step, moisture in the granulation and compression force, to produce tablets with specified properties.

The granule properties are highly collinear. Furthermore, the physical granule properties are influenced by the composition of the mixture and the process variables of the first granulation step. Therefore, the descriptor variables of the second model are highly collinear. The partial least squares regression method (PLS) will be used for the modelling because ordinary least squares regression (OLS) suffers from collinearity in the descriptor variables. PLS, just as OLS is, a least squares regression method. Several tutorials are found in literature (Geladi and Kowalski, 1986; Höskuldsson, 1988). With PLS, the regression ofthe response y is carried out on a latent factor of X, which consists of the process and composition variables and, in Model 2, on the granulation properties. The latent factors, which are linear combinations of the process and composition variables in X, are selected to describe the variance in X as good as possible and also to optimise the correlation with y, i.e. the covariance between the latent variable of X and y is maximised. After the first factor is determined, a second can be calculated, orthogonal to the first that describes the variance of y that could not be described with the first latent factor. This can be repeated until most of the variance of y is described. PLS is much used in chemometrics and has already been introduced in pharmaceutical technology (Kettaneh-Wold, 1991; Lindberg and Lundstedt, 1995). The PLS model may be evaluated with the root mean squared error (RMSE) which indicates the deviation between the measured and predicted values. For a real validation, each experiment is left out for the modelling once and predicted by the PLS model. The root mean of the predictive error sum of squares (RMPRESS) indicates how well the model predicts future response values. For a good model, RMSE and RMPRESS are comparable to the experimental error.

The main issue of this paper is the two-step approach of the process of wet granulation and tableting. The two-step approach is used to control the second step of the process by a control scheme. The modelling of the MCC mannitol tablets with ordinary least squares regression has already been presented in detail in an earlier paper (Westerhuis et al., 1996). In the present paper the PLS regression method has been used because of the highly collinear granulation properties.

Table 1
The formulation of the tablets

HPC	2–3–5%
Magnesium stearate	0.5%
Colloidal silicium dioxide	1.5%
MCC+mannitol	ad. 100%

2. Experimental

Granulations were produced according to the formulation in Table 1. The batch size was maintained on 1.05 kg. Microcrystalline cellulose

(MCC, Avicel PH102; Roquette) and mannitol (FMC cooperation) were mixed for 1 min in a Gral 10 high-shear granulator (Collette) at impeller speed 650 rpm. The percentage MCC of the total amount of MCC and mannitol was varied between 65, 75 and 90%. The HPC (Klucel; EF) solution was added, all at once, in the middle of the powder bed with the necessary amount of water. The mass was granulated for 3, 5 or 7 min at impeller speed 650 rpm and chopper speed 3000 rpm. After granulation, the mass was dried in a Kocken vacuum stove at 40°C and -1000 mbar vacuum. The moisture content of the granules was determined with a Sartorius IR humidity analyser. The granules were sieved through a 710 μm sieve on an Erweka AMD oscillator. Particle size distribution was measured by sieve analysis (Retsch 50 Hz, 20 min. sieves 600, 500, 355, 212, 125, 75 μm), and the median diameter of the mass of the granules (D_{50}) was calculated. The flow rate of 100 g granules through a funnel with an orifice of 4.5, 6.0 and 9.0 mm was measured, as were the poured and tapped specific volumes. Carr's Index: 100*((poured volume − tapped volume)/tapped volume) was calculated. The granules were admixed with 1.5% colloidal silicon dioxide (Defussa) during 1 min followed by admixing with 0.5% magnesium stearate (Otto Breyer bv) during 1 min in an Erweka mixer. After admixing, the granules were compressed into flat faced tablets (9.0 mm; 250 ma) at a compression force of 10, 20 or 30 kN on a HOKO KJ excenter press. Thirty minutes after preparation, CSs of ten tablets were measured on a Roche HT 300. DTs of six tablets were measured with disks according to USP XXII.

The six descriptor variables were: two process variables for step one (amount of water and granulation time), two process variables for step two (moisture of granules and compression force) and two composition variables (HPC and MCC). Previous experiments showed that a high water level was incompatible with a low amount of MCC as was a low level of water with a high amount of MCC. For this reason the amount of water was set dependent on the amount of MCC. The moisture of the granules was adjusted to a specific value by extra drying or moistening of the granulation in a fluid bed humidiser. After the adjustment the granules were kept in closed bags for a week to stabilize and the moisture content was rechecked. Because of the expected curvature in the response surfaces, each variable was varied at three levels. A Box–Behnken design was selected, which needed 55 experiments. In a Box–Behnken design each variable is varied on three levels to detect curvature in the response variable. No experiments at the vertices are used, which may represent extreme combinations of factors at the edge of the experimental region where problems may arise (Box and Behnken, 1960). Table 2 shows the Box–Behnken design and the measured CS, DT and ejection force (EF) of the tablets. Table 3 shows the measured granulation properties for experiments 5 and 7, which are used in the control schemes. A–C, Flow through funnel with orifice 4.5, 6.0 and 9.0 mm respectively (s); D, E, Poured and tapped volume (/ml); F, Carr's index; G, median granule diameter (D_{50}; μm); and H–N, Sieve fractions >600, 600–500, 500–355, 355–212, 212–125, 125–75, <75 (%). From experiment 14 and 15 no tablets could be obtained because of the poor compression characteristics of the granules. The PLS models were calculated with use of the PLS toolbox in matlab (PLS Toolbox for Matlab, Eigenvector Research, Manson, WA; Matlab is a registered environment for matrix calculations, The Mathworks Inc., Natick, MA).

3. Results and discussion

According to the experimental design in Table 2, granulations were made and compressed into tablets. The particle size distribution of the granules, the flow through funnels with orifices of 4.5, 6.0 and 9.0 mm and the poured and tapped volume were measured and median granule size (D_{50}) and Carr's index were calculated (Table 3). The CS, DT and the EF of the tablets were measured. CS and DT of the tablets were logarithmic transformed because of the funnel shaped heteroscedastic variance structure. Four extreme large values of EF were considered as outliers and were not used in the modelling.

Table 2
Experimental design and measured tablet properties CS, DT and EF

No.	MCC (%)	HPC (%)	Water (ml)	Time (min)	Moisture (%)	Comp. f. (kN)	CS (N)	DT (s)	EF (N)
1	75	3	500	5	3.9	20	23	11	138
2	75	3	500	5	4.3	20	48	42	110
3	75	3	510	5	4.0	20	33	24	91
4	75	3	510	5	4.3	20	38	23	91
5	75	3	510	5	3.8	20	25	11	111
6	75	3	510	5	3.8	20	35	30	92
7	75	3	510	5	3.8	20	38	34	100
8	65	3	450	7	3.8	30	55	104	126
9	65	3	450	7	3.8	10	15	2	101
10	90	3	585	3	4.0	30	11	10	50
11	90	3	585	3	4.0	10	4	2	59
12	65	3	450	3	4.2	10	23	10	235
13	65	3	450	3	4.2	30	66	291	274
14	90	3	585	7	3.7	10	—	—	—
15	90	3	585	7	3.7	30	—	—	—
16	75	5	450	5	4.0	10	14	2	99
17	75	5	450	5	4.0	30	51	138	120
18	75	5	560	5	3.8	10	17	5	74
19	75	5	560	5	3.8	30	53	400	83
20	75	2	450	5	4.2	30	75	215	358
21	75	2	450	5	4.2	10	30	2	214
22	75	2	560	5	4.0	30	51	84	99
23	75	2	560	5	4.0	10	20	6	86
24	90	3	510	5	3.3	20	22	16	81
25	90	3	510	5	4.8	20	22	15	72
26	65	3	500	5	4.8	20	61	149	117
27	65	3	500	5	3.2	20	48	65	132
28	65	3	400	5	3.1	20	44	28	141
29	65	3	400	5	4.9	20	58	72	134
30	90	3	650	5	3.4	20	6	8	53
31	90	3	650	5	5.4	20	8	15	41
32	65	2	450	7	4.0	20	49	26	153
33	65	2	450	3	4.0	20	52	42	142
34	90	2	585	7	4.4	20	9	2	68
35	90	2	585	3	4.3	20	13	4	62
36	65	5	450	3	4.0	20	37	55	138
37	65	5	450	7	4.0	20	31	32	115
38	90	5	585	7	4.2	20	6	10	44
39	90	5	585	3	4.3	20	8	16	51
40	75	3	560	7	4.5	20	65	118	79
41	75	3	560	7	3.1	20	55	54	86
42	75	3	560	3	4.6	20	57	90	88
43	75	3	560	3	3.0	20	51	33	134
44	75	3	450	3	3.0	20	51	51	134
45	75	3	450	3	4.6	20	51	38	110
46	75	3	450	7	3.1	20	43	21	127
47	75	3	450	7	4.6	20	48	47	120
48	75	2	510	5	4.8	10	22	6	92
49	75	2	510	5	4.8	30	60	125	102
50	75	2	510	5	2.8	10	11	4	91
51	75	2	510	5	2.8	30	61	48	124
52	75	5	510	5	3.1	30	57	156	110
53	75	5	510	5	3.1	10	13	6	92
54	75	5	510	5	4.5	10	23	9	85
55	75	5	510	5	4.5	30	68	421	91

Missing values (–) are caused by bad compression characteristics of the granulation.

Table 3
Measured physical granulation properties of experiments 5 and 7 given in Table 2

No.	A	B	C	D	E	F	G	H	I	J	K	L	M	N
5	1.05	2.44	6.9	1.56	1.38	13	429	10.6	21.0	37.5	25.8	3.5	0.8	0.7
7	1.02	2.34	6.37	1.78	1.58	12.7	280	1.2	4.0	16.2	53.4	19.6	2.8	2.2

A–C, Flow through funnel with orifice 4.5, 6.0 and 9.0 mm respectively (s); D–E, Poured and tapped volume (ml/g); F, Carr's index; G, Median granule diameter (D_{50}; μm); and H–N, Sieve fractions >600, 600–500, 500–355, 355–212, 212–125, 125–75, <75 (%).

The first PLS model describes CS, DT and EF of the tablets dependent on the composition of the mixture and process variables. Previous calculations showed that quadratic terms were important to CS and DT, so they were included in the model for these tablet properties but not for the modelling of EF (Westerhuis et al., 1996). Cross validation showed that three factors gave the best models for CS and DT, and only two PLS factors were needed for EF. Table 4 shows the results for the CS, DT and EF models. The percentage of explained variance of the descriptor variables and of the response are given as are the RMSE and the RMPRESS values for the three tablet properties.

The addition of the physical granule properties improves the modelling of the tablet properties CS and DT. The percentage explained variance increased from 89 to 95 for CS and from 85 to 92 for DT. The RMSE and RMPRESS values decreased for the CS and the DT. The EF model was not improved by the addition of the granule properties. Fig. 3 shows the observed CS and DT and the leave one out predictions by Model 1 and Model 2. The values predicted with Model 2 (closed circles) are closer to the observed ones than the predictions of Model 1.

Table 5 shows the most important PLS coefficients of the process and composition variables for the three tablet properties. The linear and quadratic terms of MCC and the compression force are the most important variables for CS and DT. Water is only important for CS and HPC influences only DT. For EF, both MCC and water had negative coefficients, i.e. high MCC and water levels give low EFs. The addition of the granule properties to the composition and process variables requires only one extra factor in the PLS model. Only one latent factor of the granule properties is used to improve the modelling of CS and DT. This factor is dominated by the flow times and poured and tapped volumes. Long flow times and low volumes give higher CSs and DTs.

The physical properties of the granulations are also subject to the variation introduced by the composition variables and the process variables for the first granulation step. A total of 60% of the variance in the granule properties could be explained by these design variables. The other 40% is, besides

Table 4
Results of the modelling of the EF, CS and DT for Model 1 and Model 2

	Response	No. factors	% X	% y	RMSE	RMPRESS
Model 1	CS	3	44	89	0.25	0.31
	DT	3	40	85	0.54	0.69
	EF	2	47	86	10.2	11.4
Model 2	CS	4	59	95	0.17	0.23
	DT	4	61	92	0.40	0.55

For each model, the number of PLS factors, the amount of explained variance of the descriptors (X) and the response (y), the RMSE and the RMPRESS values for the model are given.

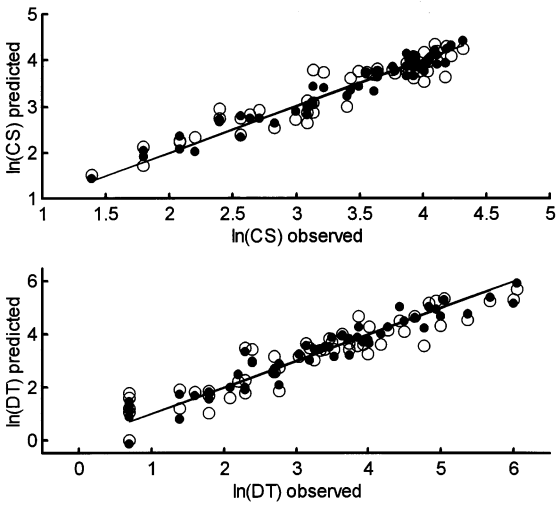

Fig. 3. Leave one out predictions of the CS and DT with Model 1 (○) and Model 2 (●).

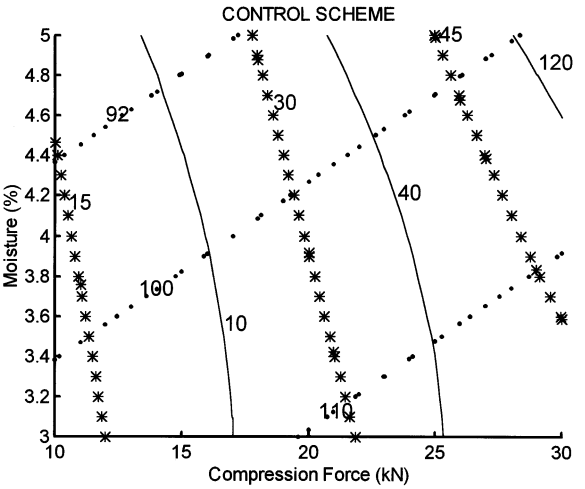

Fig. 4. Control scheme for granulation 5. Predictions for the EF (●; 92, 100, 110 N), CS (*; 15, 30, 45 N) and DT (–; 10, 40, 120 s) are given for different setting of compression force (kN) and moisture in the granules (%).

reproduction error, introduced by uncontrolled sources such as the air humidity, temperature or other unknown features. This causes the spread in granule properties when the settings of the process variables were kept the same. The extra variation in the granules, that is not introduced by the experimental design, is used to explain the variation in CS and DT that cannot be described by the variables in the experimental design.

The prediction of the physical properties of the tablets with Model 2 can differ from the ones of Model 1. Therefore, adjustment of the settings of the process variables for the second step may be necessary. This in-process control can lead to production of tablets that better meet the specified properties. A control scheme has been introduced to study the effect of the process variables of the second step on the compression of the granulations. Figs. 4 and 5 show the control scheme for two different granulations. For the granulations of experiment 5 and 7, the EF, CS and DT are given in a combined contour plot. The CS and DT are predicted with Model 2 and EF is predicted with Model 1. The compression force is varied from 10 to 30 kN and the moisture in the granules is varied from 3 to 5%. The moisture content of the granules is considered to be a variable process because it is set and rechecked to the predefined level by extra drying or humidising. The predicted EF is shown with the small dots. It increases from left to right, when the compression force increases, and the EF decreases when more moisture is present in the granulations. The CS and DT increase when both process variables are increased. With the

Table 5
Most important PLS coefficients of the process (water, compression force (Fup) and moisture in granules) and composition variables (MCC, HPC) and their squared terms for the prediction of the CS, DT and EF

Response	MCC	Water	HPC	Fup	Moisture	MCC^2	Water^2	Fup^2	Moisture^2
CS	−0.26	0.15	—	0.40	—	−0.25	−0.12	−0.11	—
DT	−0.45	—	0.31	1.13	0.24	−0.27	—	−0.17	0.20
EF	−12	−12	—	4	−4	—	—	5	—

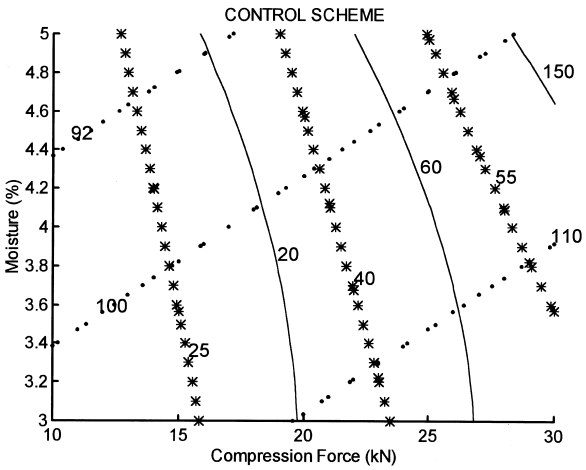

Fig. 5. Control scheme for granulation 7. Predictions for the EF (●; 92, 100, 110 N), CS (*; 25, 40, 55 N) and DT (–; 20, 60, 150 s) are given for different setting of compression force (kN) and moisture in the granules (%).

control scheme a specific setting of the process variables can be chosen to obtain tablets with specific characteristics. Experiments 5 and 7 are both centre points of the experimental design. The settings of the composition and process variables (PV1) are equal. The difference between the plots is due to the difference in granule properties. The granule properties only affect CS and DT. Experiment 7 has higher predictions for CS and DT for the same settings of the compression force and moisture in granulation. Experiment 7 has a lower mean granule size, higher poured and tapped volumes and it has shorter flow times through the funnels. The combination of these effects cause CS and DT of tablets from experiment 7 to be higher than the tablets of experiment 5.

For the production of tablets with specific properties, Model 1 is used to define settings of the composition and of the process variables of both steps. When the first granulation step has been done and the granule properties have been measured, the control scheme can be used to adjust the settings of the step two process variables.

4. Conclusion

For modelling of the two-step tablet manufacturing process, two models are used. The first model relates the CS, DT and EF to the composition variables and process variables of both steps. In the second model the physical properties of the intermediate granules, are included. The first model can be used at the start of the process to find settings for the process variables and the composition of the tablet mixture that produce tablets with specific properties. Model 2 has to be used, in everyday production, for each new granulation batch. The granule properties may differ from batch to batch due to uncontrolled sources such as air humidity, temperature or other unknown features. With Model 2 these differencesare taken into account, and the CS and DT are predicted better than with Model 1. Model 2 offers the possibility to use a control scheme for each new batch of granulation, to adjust the process variables for the tableting step, moisture in the granulation and compression force, to produce tablets with specified properties. Because of this adjustment, in-process control is possible and tablets can be produced that better meet the specifications. The control scheme gives predictions for all tablet properties at various settings of the process variables for the second tableting step for a specific granulation.

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