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Optimisation of the composition and production of mannitol/microcrystalline cellulose tablets

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Abstract

Mixtures of mannitol and microcrystalline cellulose (MCC) were investigated on a small-production scale by granulation in a high-shear mixer and compression into tablets. For both excipients only a few cases of incompatibilities with active ingredients are known. Tablets with only MCC as the filler excipient have mostly inferior strength and tablets of only mannitol disintegrate slowly. However, a combination of both excipients resulted in sufficiently rapid disintegrating tablets with acceptable strength. The composition of the tablet mixture and the process of tablet manufacturing were optimised using statistical techniques. Next to the effects of the amounts of MCC and hydroxypropylcellulose (HPC) in the composition, the effects of the amount of water and the granulation time were evaluated. For the production of tablets both the effects of moisture content in the granules and compression force were studied. Simultaneous optimisation of crushing strength, disintegration time and ejection force of the tablets was carried out to find optimal regions in the design space for these tablet properties. In conclusion, mannitol/MCC mixtures can be considered as an interesting alternative in case classical excipients cannot be selected in formulation development, due to chemical incompatibilities with active ingredients or inferior physical characteristics.

Keywords: Granule and table properties; Mannitol; Microcrystalline cellulose; Optimisation; Statistical design

1. Introduction

Wet granulation is a process of size enlargement and is generally applied in the pharmaceutical industry to prepare powdered materials for

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capsules and tablets. Several strategies have been used to optimise the process of granulation and tablet manufacturing (Doonbos and de Haan, 1995; Bohidar, 1991; Chariot et al., 1988; Wehrlé et al., 1994; Lindberg et al., 1985; Gould, 1984; Vojnovic et al., 1994). Most of the research on granulation in high-shear mixers has been carried out with lactose and calcium-hydrogen-phosphate as the major filler excipients in the blend. Both calciumphosphate and lactose formulations can give rise to physical and chemical problems, the latter particularly in formulations with drugs that give the Maillard decomposition reaction. Both MCC and mannitol are relatively inert and only a few cases of incompatibilities with active ingredients have been reported.

The aim of this study was to evaluate the applicability of mannitol/MCC mixtures and to optimise the composition and production of the tablets for their granulating and tableting properties using statistical optimisation techniques.

2. Methods

2.1. Design of experiments

The design of experiments in this study was divided into three steps: the screening of important process variables, the robustness of the process and the final experimental design. The final design was restricted to 40 granulation experiments aimed to give quantitative information about the effect of only six process or composition variables on the granule and tablet responses.

An extensive list of all variables that affect the process of granulation and tableting is based on everyday experience. From this list some variables were chosen for further research, others were kept constant at a specified level. The following criteria were used to come to a selection of important variables: known for its high influence, traditionally varied to solve technological problems, easy to control and vary, meets peoples interests, affects nearly all responses. Screening experiments finally resulted in the selection of six variables and their valid ranges.

An essential step in the optimisation process is to establish the robustness (reproducibility) of the manufacture of granules and tablets against disturbances in variables that are assumed to stay constant. If the process is not robust, effects of process variables are more difficult to detect.

The six chosen process and composition variables were set at specific levels for the final experimental design. Because of the expected curvature in the response surfaces, each variable was varied at three levels. A Box-Behnken design was selected, which only needed 55 experiments (Box and Behnken, 1960). Fig. 1 shows a three variable BB design. No experiments at the vertices of the cubic region are necessary. This can be advantageous because the corners of the cube represent extreme combinations of factors at the edge of the experimental region where physical-chemical problems may arise.

The six variable BB design used, is shown in Table 1. The ± 1 stands for the high and low level of the specific variable, and 0 stands for the medium level. The number of batches in each row that have to be granulated is given in the last column. Two of the four process variables, compression force and moisture in the granules, are not applied at the production of the granulate. These process variables can be varied using the same batch of granules. Therefore, the number of

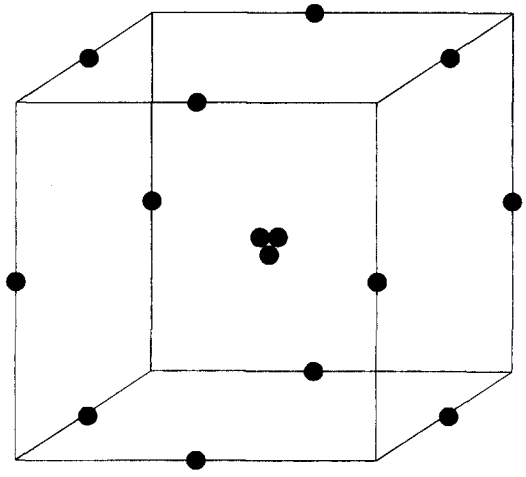

Fig. 1. A three variable Box Behnken design. Each variable is varied on three levels.

Table 1
Box Behnken design with four process and two composition variables

MCC	HPC	Water	Time	Moisture	Fup	No. of Batches
±1	±1	0	±1	0	0	8
0	±1	±1	0	±1	0	4
0	0	±1	±1	0	±1	4
±1	0	0	±1	±1	0	4
0	±1	0	0	±1	±1	2
±1	0	±1	0	0	±1	4
0	0	0	0	0	0	7

batches can be diminished from 55 to only 33 batches. Experiments from the same granulate are not fully independent, but because the production of the granulate is very reproducible, this drawback is considered acceptable. Table 2 shows the variables and levels that were set. Two composition variables are varied, the amount of MCC and HPC in the blend. The other four variables, the amount of water added to the mixture, granulation time, moisture level of the granules and compression force (Fup), define the process. The moisture level of the granulate was set to a specific value using methods including drying in a Kocken vacuum stove. The binary mixture of MCC and mannitol can be represented by only one variable. The calculated effect of MCC, therefore, is not from the pure component. It points out the effect of the combination of MCC and mannitol.

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 according to a previous defined experimental relation given in Table 2.

Table 2
The levels of the variables in the Box Behnken design

Process variables	Low level	Medium level	High level
MCC (%)	65	75	90
Water (ml)	110+4.5* MCC	110+5.3* MCC	110+6.0* MCC
HPC (%)	2	3	5
Time (min.)	3	5	7
Moisture (%)	3	4	5
Fup (kN)	10	20	30

2.2. Statistical analysis of the results

The use of regression analysis in this study has two main purposes, process investigation and optimisation of tablet properties. To obtain regression models that describe the data well and give good predictions, a well-defined strategy is followed. The strategy is divided into three steps.

(1) Outlier selection.
(2) Model selection.
(3) Model evaluation.

The data measured is modelled to a linear model with linear, quadratic and interaction terms. The complete model is defined as follows:

$$Y = a + b_1\boldsymbol{x}_1 + \cdots + b_6\boldsymbol{x}_6 + c_1x_1^2 + \cdots + c_6\boldsymbol{x}_6^2 + d_{12}\boldsymbol{x}_1\boldsymbol{x}_2 + \cdots + d_{56}\boldsymbol{x}_5\boldsymbol{x}_6$$

In this model the intercept a gives the response value Y in the centre of the design where all variables $\boldsymbol{x}_1 \ldots \boldsymbol{x}_6$ are set to zero. The parameters b, c and d are regression coefficients for the linear, quadratic and two-factor interaction terms, respectively.

2.2.1. Outlier selection

The residuals of the complete model are examined for outliers with an envelope plot of the Studentized residuals. Studentized residuals have mean zero and unit variance and they are corrected for the influence of the position in the

design (Myers, 1989). The residuals are plotted in an envelope plot (Atkinson, 1985). When residuals fall outside the envelope, they are removed as outliers.

2.2.2. Model selection

Model selection starts with the determination of the complexity of the model. The successive addition of the linear, quadratic and interaction terms is evaluated with a F-test. The adjusted correlation coefficient ($R^2_{adj.}$) and Amemiya's prediction criterium (PRC) are calculated for these models (Judge et al., 1985). R^2_{adj} gives the variation in the data accounted for by the regression model. The PRC compares mean squared errors of the models. Both are corrected for the number of observations and parameters in the model. For a good model, R^2_{adj} is close to 1 and PRC is as low as possible.

Variable selection is done to use only those variables that influence the response. The models are stripped one group at the time. Groups of a specific variable are formed by its linear and quadratic term and all interaction terms. Groups are stripped until they all are significant at the 0.05 level. The P-value shows the significance for the F-test for the Mean Square of the Type II Sum of squares explained by the group and the Mean Square of the residuals (SAS/STAT User's Guide, 1990). In the evaluation of the models R^2_{adj} and PRC are included. The model with optimal R^2_{adj} and PRC values will be chosen as the final model. However, the figures may be ambiguous. They are not always both optimal for the same model. When this is the case, selection of the final model has to be made on additional arguments. The final model was tested for lack of fit (Myers, 1989).

2.2.3. Model evaluation

After estimation of all parameters in the model, several plots of responses against process variables can be drawn and evaluated. From these plots, optimal combinations of the process variables can be found for the tablet responses to meet given criteria. For prediction properties, the PRESS (prediction error sum of squares) is calculated. If the root mean of the PRESS, the Root Mean Squared Error of the model and the reproduction error of the centre point are of comparable size, the model can predict new response values with the same precision as described by the data.

Table 3
The formulation of the tablets

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

In the process of tablet making a number of demands have to be satisfied. Usually, optimal values for different responses are not obtained at the same settings of the process and composition variables. Overlay contour plots can be drawn for several responses in the experimental space, to find regions in the experimental space that fulfil restrictions of tablet properties.

3. Experimental

3.1. Granulation and compression process

Granulations were prepared according to the formulation in Table 3. 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 HPC (Aqualon) solution was added 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. From the granules 400 g was taken and admixed with 1.5% colloidal silicon dioxide (Defussa) for 1 min followed by admixing with 0.5% magnesium stearate (Otto Breyer B.V.) for 1 min in an Erweka mixer. After admixing, the granules were compressed into flat faced tablets (9.0 mm; 250 mg) at a compression

Table 4
Final models for the ejection force, crushing strength and disintegration time of mannitol MCC tablets.

Response	Ejection force (N)		Crushing strength (N)		Disintegration time (s)	
Outliers	3		—		—	
R^2	0.9009		0.8854		0.9144	
p (Lack of fit)	0.96		0.71		0.69	
Intercept	101.48		36.51		3.22	
MCC	−28.9	***	−11.08	***	−0.658	***
Time	−5.1	*				
Fup	4.55		18.62	***	1.687	***
Moisture	−8.09	**	5.54	**	0.489	***
HPC	−4.56	**			0.231	***
Water	−12.3	***	0.54		0.278	**
MCC^2			−6.77	***	−0.241	**
Fup^2			−3.53		−0.315	*
$Moisture^2$			6.32	*	0.527	**
$Water^2$			5.71	**	0.315	**
MCC* fup	39.47	***	−6.34	*	−0.378	*
MCC* mositure			−5.15	*	−0.357	*
MCC* HPC					0.158	*
MCC* water			−4.10	*	−0.288	*
Time* fup	59.00	***				
RMSE	12		7.6		0.48	
s	17		8.5		0.53	
RMPRESS	23		9.2		0.55	
	$t1$: 70		$t1$: −5		$t1$: 0.285 (1 s)	
	$t2$: 103		$t2$: 13		$t2$: 2.522 (12 s)	

Outliers, R^2, and lack of fit probability are given. Further model parameters are given with their significance (*$P<0.05$, **$P<0.01$, ***$P<0.001$), and RMSE, error of reproduction (s) and RMPRESS values. $t1$ and $t2$ give indications of properties for the tablets with bad compression properties.

force of 10, 20 or 30 kN on a HOKO KJ excenter press.

3.2. Granule and tablet properties

Before admixing the granules with colloidal silicon dioxide and magnesium stearate, the particle size distribution was measured by sieve analysis (Retsch 50 Hz, 20 min. sieves 600, 500, 355, 212, 125, 75 μm), and the mean diameter of the granules was calculated. The flow rate of 100 g granulate through a funnel with an orifice of 4.5 mm was measured, as were the poured and tapped specific volumes. During tableting, ejection forces of the tablets were registered with a Siemens Oscilloreg. At 30 min after preparation, the crushing strengths of ten tablets were measured on a Roche HT 300. Disintegration times of six tablets were measured with disks according to USP XXII.

4. Results and discussion

Robustness experiments showed that the process of granulation and tablet making is in control. The reproducibility of the tablet responses was considered good enough to continue the study.

4.1. Tablet properties

Tablets were compressed from the granules. One granulation experiment (90% MCC, 3% HPC, 585 g H_2O, 4% moisture, granulation time 7 min.) turned out to have extremely poor compressibility properties. This batch was supposed to be tableted at two different compression forces. No tablet properties could be obtained for these experiments. Table 4 gives the characteristics of the models for the tablet responses.

4.1.1. Disintegration time

The analysis of the results of the disintegration time will be used to show the statistical route mentioned earlier in this paper and is therefore shown in detail. A logarithmic transformation was used to correct for the heteroscedastic measurement error. No outliers were removed.

Scheme 1 shows the detailed results of the model building. A complete model with linear, quadratic and interaction terms was selected to fit the disintegration time data. A variable selection was done on this model. The granulation time variable group provides no significant addition to the model ($P = 0.3969$). The whole variable group was removed. The new complete model shows no insignificant variable groups ($P < 0.05$). The second model has an improved PRC, but R^2_{adj} decreased a little. Comparing both models the second was selected because it is simpler than the first model. Looking to the model in detail, only the MCC group of interactions is significant (*P*-values PROB > |T| below 0.05). The other interactions were removed from the model as was the quadratic HPC term ($P = 0.25$). The final model (Table 4) has a lower R^2_{adj}, but the PRC and PRESS values improved and it shows no lack of fit.

The amount of MCC has a reducing effect on the disintegration time. Higher compression forces give tablets with shorter disintegration time. The effect of the other variables depends on the level of MCC. Fig. 2 shows the disintegration time as a function of compression force and amount of MCC. High levels of MCC give tablets that disintegrate fast as do tablets compressed at 10 kN. At a low MCC amount, the effects of compression force, amount of water and moisture in the granules are higher than at high levels of MCC.

4.1.2. Other tablet properties

Table 4 shows models for the ejection force and crushing strength of mannitol MCC tablets.

MCC has to be below 85% and the compression force must exceed 15 kN to obtain tablets with crushing strengths of at least 40 N. Fig. 3 shows the crushing strength as a function of MCC and compression force. Predictions of negative crushing strengths are caused by extrapolation of the quadratic model at the outer regions of the experimental space.

For the ejection force of the tablets, three observations were selected as outliers. Fig. 4 shows an obvious effect of the amount of MCC and compression force on the ejection force. When more water is added, the ejection force decreases. For all tablet properties the Root Mean PRESS values are of comparable size to the RMSE and the reproducibility.

At the end of Table 4, indications are given for the tablet properties of the experiments with bad compressibilities ($t1$, 10 kN; $t2$, 30 kN). Although the models are extrapolating, they show that the tablets would be very weak.

4.2. Granule properties

The granule properties were also modelled on the process and composition variables. The compression force is irrelevant for the granule proper-

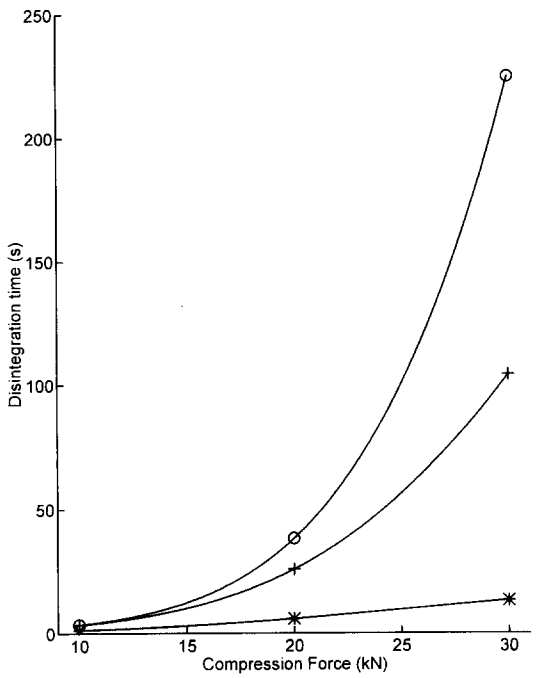

Fig. 2. Prediction of the ejection force of mannitol MCC tablets, dependent of the amount of MCC and the compression force. (MCC: ○ = 65%, + = 75%, * = 90%; HPC 3%, granulation time 5 min, moisture in granulate 4%, water at its medium level).

ln disintegration time

Regressors	R2	F	p	R2adj	PRC
linear	0.8026	66.302	0.0000	0.7768	0.5149
quadratic	0.0801	6.619	0.0003	0.8475	0.3870
cross	0.0669	2.209	0.0385	0.8951	0.3267
TOTAL	0.9496	17.432	0.0000		

full model

Factor	SSII	MS	F	p		
MCC	25.4282	3.6326	16.9917	0.0000	R2	= 0.9496
water	5.3801	0.7686	3.5951	0.0082	PRC	= 0.3267
time	1.6371	0.2339	1.0939	0.3969	R2adj	= 0.8951
Fup	67.3874	9.6268	45.0296	0.0000	LOF	= 0.7491
moisture	4.8328	0.6904	3.2294	0.0140		
HPC	5.3739	0.7677	3.5909	0.0082		

full model (-time)

Factor	SSII	MS	F	p		
MCC	25.3155	4.2192	19.3384	0.0000	R2	= 0.9341
water	4.8740	0.8123	3.7232	0.0064	PRC	= 0.3046
Fup	67.1179	11.1863	51.2711	0.0000	R2adj	= 0.8929
moisture	4.9530	0.8255	3.7836	0.0058	LOF	= 0.7341
HPC	5.3972	0.8995	4.1229	0.0035		

ANALYSIS OF VARIANCE

SOURCE	DF	SS	MS	F-value	PROB>F
MODEL	20	98.9851	4.94925	22.6843	0.0000
ERROR	32	6.98175	0.21818		
TOTAL	52	105.967			

RMSE = 0.46710 PRESS = 21.33245

VARIABLE	PARAMETER ESTIMATE	STANDARD ERROR	T FOR H0: PARAMETER=0	PROB>|T|
intercept	3.2160	0.06416	50.12450	0.0000
MCC	-0.6482	0.09878	-6.56183	0.0000
water	0.2556	0.09386	2.72311	0.0052
Fup	1.6419	0.10439	15.72798	0.0000
moisture	0.4919	0.11846	4.15281	0.0001
HPC	0.2965	0.11008	2.69323	0.0056
MCC^2	-0.2515	0.09320	-2.69855	0.0055
water^2	0.3065	0.12420	2.46788	0.0096
Fup^2	-0.2671	0.15280	-1.74833	0.0450
moisture^2	0.4960	0.17399	2.85049	0.0038
HPC^2	-0.0523	0.07685	-0.68069	0.2505
MCC*water	-0.2896	0.12113	-2.39099	0.0114
MCC*Fup	-0.3767	0.16076	-2.34306	0.0128
MCC*moisture	-0.3550	0.15626	-2.27170	0.0150
MCC*HPC	0.1493	0.08598	1.73599	0.0462
water*Fup	-0.2138	0.15835	-1.35010	0.0932
water*moist.	0.0977	0.13306	0.73414	0.2341
water*HPC	0.1594	0.10233	1.55816	0.0645
Fup*moisture	0.1670	0.18567	0.89956	0.1875
Fup*HPC	0.1450	0.07703	1.88236	0.0345
moisture*HPC	0.0439	0.13134	0.33459	0.3701

New model

SOURCE	DF	SS	MS	F-value	PROB>F
MODEL	13	96.8979	7.45369	32.0539	0.0000
ERROR	39	9.069	0.23254		
TOTAL	52	105.967			

RMSE= 0.4822 R2 = 0.9144 PRESS = 16.38105
PRC = 0.2895 LOF= 0.69 R2adj = 0.8859

Scheme 1. Detailed results of the modelling of the logarithmic scaled disintegration time.

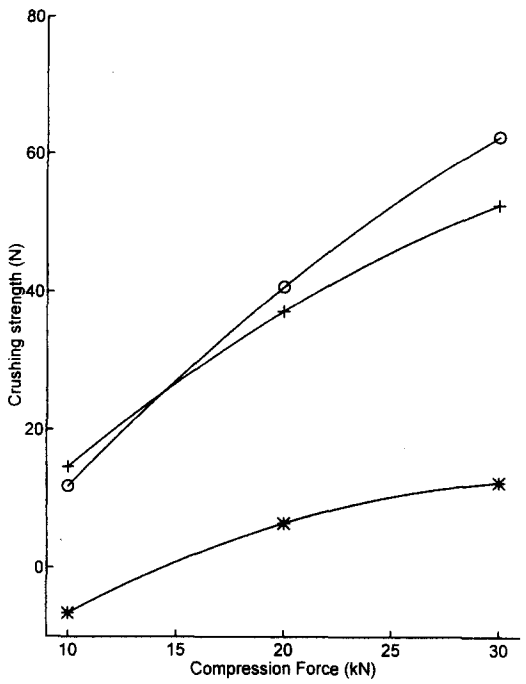

Fig. 3. Prediction of the crushing strength of mannitol MCC tablets as a function of the amount of MCC and the compression force. (MCC: ○ = 65%, + = 75%, * = 90%; HPC 3%, granulation time 5 min, moisture in granulate 4%, water at its medium level).

ties and is therefore not taken into account. Table 5 shows mathematical models constructed to fit granule responses.

The mean granule size is calculated from particle size distribution measurements. Only linear terms of the amount of water and concentration of the binder are used in this model. Both terms have a large positive effect on the response, so the mean particle size increases with increasing amounts of water and concentration of binder. With this simple model the data is fitted well and predictions are also good.

The percentage of fines indicates the material that has not been granulated or is segregated during handling. The highest percentage can be found at low levels of water and HPC. The number of fines decreases when more water or HPC is added. However, when both are high, the percentage of fines increases again.

For the specific volumes poured and tapped, the same variables are important in the models. The highest specific volumes are obtained at a medium level of MCC and a low amount of water. The flow through a funnel with an orifice of 4.5 mm diameter is modelled with a full quadratic model. A strong curvature of the flow in the MCC direction is observed. The lowest flow is reached at medium levels of MCC with large amounts of HPC and water.

4.3. Multi criteria optimisation

Crushing strength, disintegration time and ejection force of the tablets are examined simultaneously. Overlay contour plots of the tablet responses are given in Fig. 5. Each subplot shows the crushing strength, disintegration time and ejection force of the tablets dependent on compression force and MCC. In the horizontal direc-

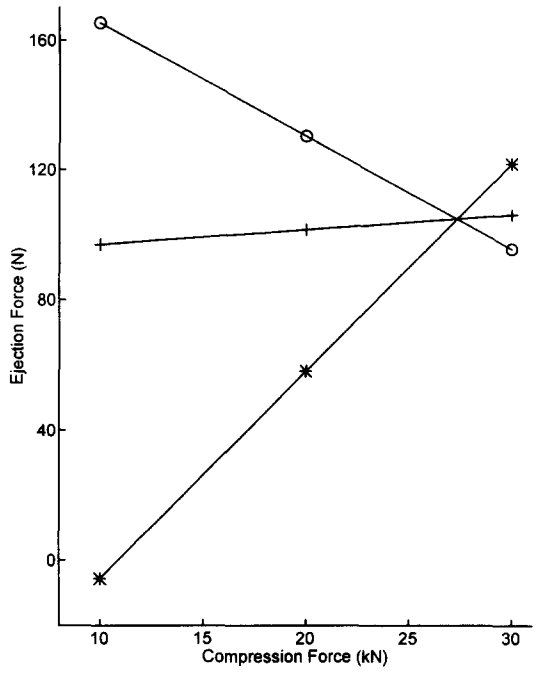

Fig. 4. Prediction of the disintegration time of mannitol MCC tablets as a function of the amount of MCC and the compression force. (MCC: ○ = 65%, + = 75%, * = 90%; HPC 3%, granulation time 5 min, moisture in granulate 4%, water at its medium level).

Table 5
Final models for mean diameter, % fines, specific volumes poured and tapped and flow of mannitol MCC granulates

Response	Mean granule size (μm)	Fines (%)	$Vol._{Poured}$ ($ml \cdot g^{-1}$)	$Vol._{Tapped}$ ($ml \cdot g^{-1}$)	Flow ($g \cdot s^{-1}$)
Outliers	—	—	—	—	—
R^2	0.86	0.71	0.76	0.75	0.91
P (Lack of fit)	0.88	0.37	0.77	0.76	0.73
Intercept	353.58	2.18	1.65	1.50	1.079
MCC		−0.0199	−0.013	−0.008	
Moisture					−0.016
Time		−0.41 *	−0.018	−0.017	−0.005
HPC	64.2 ***	−0.37 **	−0.070 **	−0.047 **	−0.047 ***
Water	156.8 ***	−1.06 ***	−0.051 **	−0.022	−0.100 ***
MCC^2			−0.102 ***	−0.097 ***	0.093 ***
$Moisture^2$					−0.058 **
$Time^2$			0.056 *	0.054 **	−0.046 **
HPC^2			0.024 *	0.016	
$Water^2$		1.02 ***	0.057 **	0.042 *	−0.026 *
MCC* moisture					0.045 **
MCC* time					0.027 **
MCC* HPC					−0.025 **
MCC* water					0.027 *
Time* water		0.66 *			
HPC* water		1.30 ***			
RMSE	55	0.92	0.08	0.07	0.047
s	71	0.66	0.09	0.08	0.053
RMPRESS	57	1.02	0.09	0.075	0.059

Outliers, R^2, and lack of fit probability are given. Further model parameters are given with their significance (*$P<0.05$, **$P<0.01$, ***$P<0.001$) and RMSE error of reproduction (s) and RMPRESS values.

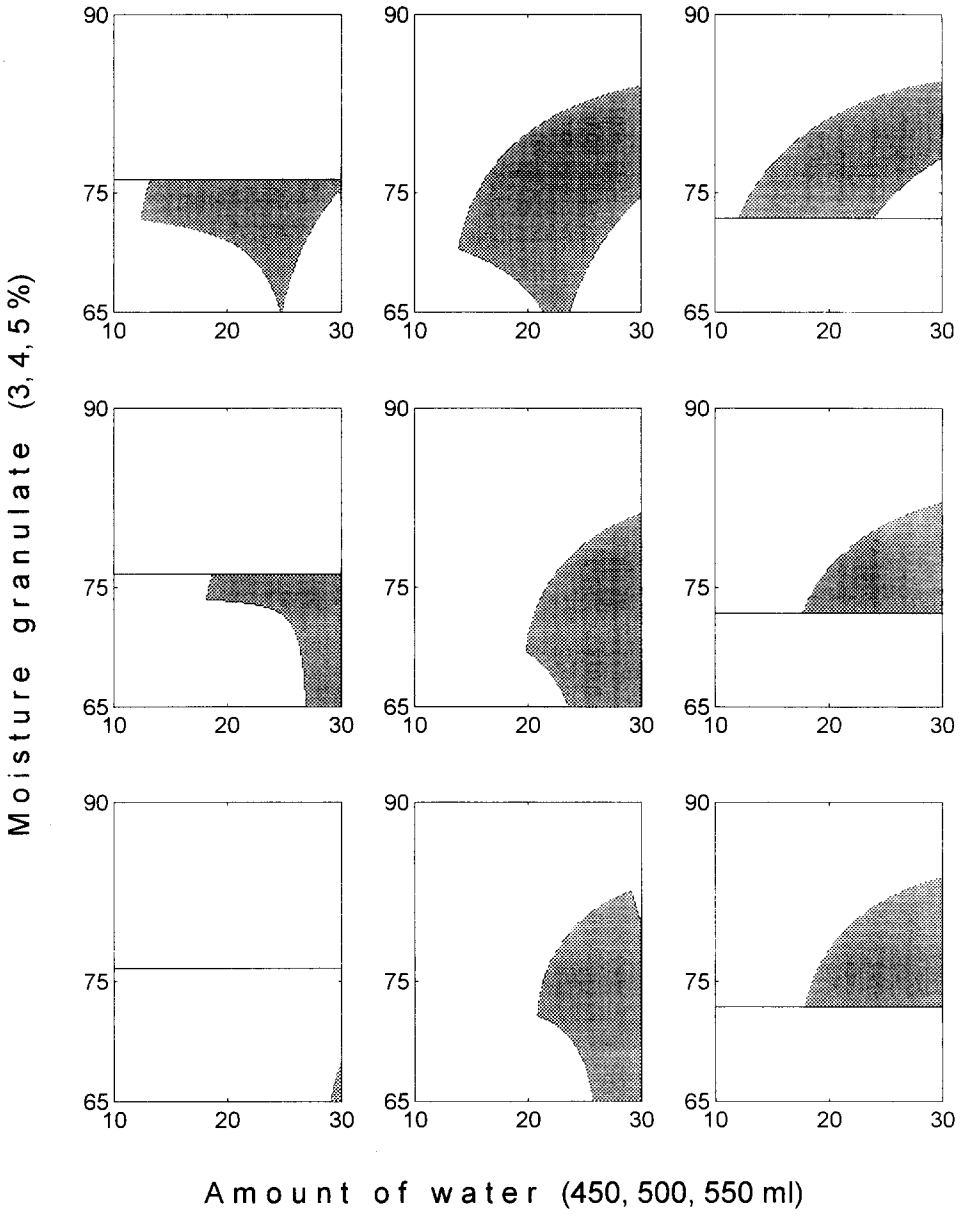

Fig. 5. Overlay contour plots of crushing strength, disintegration time and ejection force. In each plot compression force (10, 20, 30 kN) and MCC (65, 75, 90%) are varied. Horizontally water changes from 450 to 550 ml and vertically moisture in the granulate (3, 4, 5%). The dark area features tablets with crushing strengths >40 N, disintegration times <5 min and ejection force <110 N. (HPC 5%, granulation time 5 min.).

tion, water is varied from 450 to 550 ml and in the vertical direction the moisture in the granules is varied from 3 to 5%. The gray part of the plots have acceptable values for all tablet responses: crushing strength above 40 N, disintegration times below 5 min and ejection forces below 110 N. In each constrained plot (because of the MCC water relation) the upper left corner gives tablets that

Table 6
Predicted properties of mannitol MCC tablets at some settings of the composition and process variables

MCC (%)	HPC (%)	Moisture (%)	Water (g)	Fup (kN)	Time (min)	Crushing strength (N)	Disintegration time (s)	Ejection force (N)
70	3	3	525	25	5	51	105	102
70	5	3	525	25	5	51	142	92
70	3	5	525	20	5	57	168	84
70	5	5	525	20	5	57	228	58
80	3	3	550	25	5	44	88	95
80	5	3	550	25	5	44	163	85
80	3	5	550	20	5	43	84	75
80	5	5	550	20	5	43	156	66

are too soft, the lower left corner gives ejection forces of more than 110 N and the lower right corner gives tablets with long disintegration times. HPC is set at 5% and the granulation time at 5 min. When less HPC is added, ejection forces increase.

To result in good mannitol/MCC tablets, MCC should be between 70 and 80%, water should be about 525 g or higher—dependent on the MCC amount, HPC should be 4–5% and compression force must be about 25 kN. When the granulate contains more than 5% moisture the tablets become stronger and a compression force of 20 kN is satisfactory. More compression force or less MCC gives stronger tablets. Table 6 shows predicted tablet properties for some settings of process variables. More HPC decreases the ejection force, but if enough water is added during granulation, HPC can be kept low.

5. Conclusion

Mixtures of MCC and mannitol in tablets can be used as a good alternative to classical filler excipients. The amounts of MCC, HPC and water strongly affect tablet properties as do compression force and moisture of the granulate. Granulation time hardly affects tablet properties. The amount of HPC does not influence the crushing strength of tablets. The combination of MCC and mannitol gives tablets with short disintegration times and sufficient strength. For tablets with crushing strengths more than 40 N, disintegration times less than 5 min and ejection forces less than 110 N, the amount of MCC should be between 70 and 80%, the compression force must be 25 kN and the amount of water should be at least 525 g, dependent on the MCC amount. When the moisture content in the granulate is 5%, a compression force of 20 kN appears adequate.

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