Direct Pelletization in a Rotary Processor Controlled by Torque Measurements. II: Effects of Changes in the Content of Microcrystalline Cellulose

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ABSTRACT In the present study we investigated the effect of changes in the content of microcrystalline cellulose (MCC) on a direct pelletization process in a rotary processor in which the liquid addition was terminated once a certain increase in torque was produced. Nine different mixtures of MCC and lactose with MCC contents varying from 10% to 100% (w/w) were pelletized using 6 different torque increase levels, and the changes in pellet characteristics were investigated. The pellet characteristics investigated were pellet shape, size, and size distribution as well as the water content of the pellets at the end of liquid addition. To produce spherical agglomerates with suitable characteristics in a reproducible way, a content of at least 20% (w/w) MCC was found necessary. Linear correlations were found between the MCC content and the water content and between the torque increase and the water content, showing that the torque increase is suitable to control the process. A higher torque increase or a higher MCC content was found to increase the water content independently of each other.

INTRODUCTION

Because of its unique properties, microcrystalline cellulose (MCC) is a key excipient in the production of pellets by wet granulation in a rotary processor (fluidized bed rotor granulator) (1) and by the extrusion/spheronization process (2).

In the rotary processor, the pellets can be prepared by a single-step process by aqueous granulation (3-5). Pellets produced by this method were reported to be of the same quality as pellets produced by the conventional multi-step extrusion/spheronization process (6).

When preparing pellets in a rotary processor, the choice of MCC grade is not critical and has only a small effect on pellet characteristics when changing the MCC type (7). On the other hand, the amount of MCC in a formulation has been reported to be crucial for the success of the formation of pellets (3,7). Generally, an amount of 15% to 30% (w/w) MCC has been reported necessary to produce spherical agglomerates with suitable properties (1,8). The actual amount needed seems to depend on the other excipients, as well as on the type of rotary processor. More MCC resulted in larger agglomerates, a wider size distribution, and less friable (3) and more spherical (9) agglomerates. The porosity of the agglomerates was not affected by the content of MCC in the range of 10% to 30% (w/w) (8).

The amount of MCC needed to produce pellets is influenced by the properties of the other excipients. The most investigated formulation is MCC and lactose, but others have been used. The solubility of the excipients in the binder liquid is influential, and the MCC content was found to be more critical when using the water-soluble lactose compared to the insoluble calcium hydrogen phosphate (4). The

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particle size of both water- and insoluble excipients is also influential (4,7), with decreasing particle-size-producing pellets of a less uniform particle size and an increased amount of oversized pellets and fines.

In most cases, water is used as the binder liquid. An increasing amount, leading to higher water content in the formulation, resulted in larger agglomerates (5,10-12).

The size distribution of pellets produced in a rotary processor seems to depend on the type of equipment used and was found both to increase (3) and decrease (10) when more binder liquid was added.

The water content in the formulation has to be tightly controlled in order to control the pellet size (5,13,14). It is therefore advantageous to establish an end-point control system that enables the formulation to reach an optimal water content and thereby to produce spherical pellets of a desired size with a narrow size distribution.

The use of torque measurements to control production of pellets in a rotary processor has been investigated previously (5), and it was found that torque-increase measurements were suitable to control the production of pellets because the water content of the mass is reflected in the torque. Random variations in the moisture content of the materials can thus be compensated for by stopping the liquid addition at a certain level of torque. Because the torque has been found to be influenced by the rotation speed of the friction plate and by the batch size, there is no general correlation between torque increase, water content, and pellet size for a certain formulation. If these process variables are kept constant, there seems to be a close correlation between the torque increase and the pellet size. In the previous study, this correlation was demonstrated for only 1 formulation containing MCC and lactose (1:1).

The aim of the current study was to investigate the effect of changes in the MCC content on pelletization in a rotary processor using torque end-point detection. The influence of changes in the MCC content on pellet characteristics at different torque increase levels was examined.

MATERIALS AND METHODS

Materials

α-Lactose monohydrate (Pharmatose, type 200M; DMV International, Veghel, the Netherlands) and MCC (Avicel, type PH-101; FMC International, Cork, Ireland) were used as starting materials. The particle size distributions by volume were the same as previously described (5). Purified water (European Pharmacopoeia) was used as binder liquid.

Equipment

The instrumented rotary processor (Glatt GPCG-1; Glatt, Dresden, Germany) applied in previous experiments (5) was used for all the experiments. The instrumentation allows recording of the torque of the friction plate as well as the inlet and outlet air temperature, the product temperature, the fluidizing air flow rate, and the air gap pressure difference.

PELLETIZATION PROCEDURE

Set-Up Phase

A total of 750 g of the excipients was mixed manually, sieved through a 1.0-mm sieve, and loaded into the product chamber of the rotary processor, which had been preheated by running without product for 12 minutes. After the fluidizing air flow was initiated, the friction plate was elevated to adjust the air gap pressure difference. Once the desired air gap pressure difference was reached, the rotation of the friction plate was turned on and set to 900 rpm. Temperature and flow rate of the fluidizing air were set to 40°C and 90 m^3/hour, respectively, in all experiments.

Liquid Addition Phase

Purified water was then sprayed tangentially into the moving powder at a rate of 30 g/minute using a pneumatic atomizer with a 1.0-mm nozzle diameter, an air dome setting of position 3, and an atomizing

air pressure of 2.0 bar. The position of the air dome determines the angle of the spray cone, and the spray cone was found visually to be suitable when using position 3. The liquid addition was continued until the ΔTq, computed as the difference between the current torque value and the minimum torque value, as previously described (5), had reached the desired value.

Wet Massing Phase

Immediately after stopping the liquid addition, two samples of about 3 to 5 g were drawn with the sample thief of the equipment for the determination of the water content, and the nozzle was removed. Wet massing was continued for 6 minutes.

Drying Phase

The wet pellets were tray-dried at room temperature until constant mass was attained. For the determination of the water content, samples were dried in an oven at 105°C until constant mass, and the water content percentage was then calculated on a dry mass basis.

Pellet Characterization

The size distribution of the dried pellets was estimated by sieve analysis of a sample (n = 1) of about 75 g drawn by scooping, and the geometric weight mean diameter (d_{gw}) and the geometric standard deviation (s_g) were calculated. A series of 13 ASTM standard sieves (Retsch, Haan, Germany) in the range of 180-2800 μm was vibrated for 15 minutes by a Fritsch Analysette 3 vibrator (Fritsch, Idar-Oberstein, Germany).

Photographs of pellets from selected experiments were taken with a scanning electron microscope (SEM) (Jeol JSM 5200; Jeol, Tokyo, Japan). Image analysis was performed as previously described (15) on pellets from selected experiments. The shape of the pellets was characterized by their aspect ratio, calculated as the length of the pellets divided by the width found at a 90º angle to the length.

Experimental Design

Nine different formulations of MCC and lactose with MCC contents varying from 10% to 100% (w/w) were pelletized in duplicate in a randomized order. No other excipients were used. The ΔTq value was varied at 2 levels for 7 of the formulations and at 6 different levels for 2 of the formulations giving a total of 52 experiments (Table 1). The response variables were geometric weight mean diameter (d_{gw}), geometric standard deviation (s_g), and the aspect ratio of the pellets and water content of the mass at the end of liquid addition. Additionally, the surface structure of pellets from selected experiments was investigated qualitatively using an SEM.

Statistical analysis was performed using STATISTICA software (Version 5.1; StatSoft, Tulsa, OK). The influence variables MCC and ΔTq were coded according to Table 2. A full second-order polynomial (Eq. 1) was fitted to the individual response variables by multiple linear regression for the 44 runs including more than 15% (w/w) MCC.

$$y = b_0 + b_1 x\, MCC + b_2 x\, \Delta Tq + b_{11} x\, MCC^2 + b_{22} x\, \Delta Tq^2 + b_{12} x\, MCC\, x\, \Delta Tq \qquad (Eq.\ 1)$$

For certain subsets of the runs, simple regression analysis was performed to compare the results of this study with those of other studies.

RESULTS AND DISCUSSION

The experimental settings and the results of the pelletization experiments are shown in Table 1. The range of ΔTq values was chosen as the widest possible range that allowed a controllable process. Torque increases below 0.2 N•m were too small to be measured accurately, and values above 1.2 N•m resulted in uncontrollable agglomerate growth and snowballing. The 2 ΔTq values (0.4 and 0.8 N•m) used with all 9 formulations were chosen based on previous experiments (5).

Table 1: Effects of MCC content and torque increase (ΔTq) on pellet size (d_{gw}), pellet size distribution (s_g), water content at the end of liquid addition, and pellet shape (aspect ratio)

Exp.#	MCC content (%(w/w))	ΔTq (N•m)	d_{gw} (μm)	s_g	Water content (%) (n=2)	Aspect Ratio
1	10	0.4	366	2.54	35.6	
2	10	0.4	272	3.22	27.1	
3	10	0.8	1515	1.88	35.4	
4	10	0.8	1313	3.31	35.2	
5	15	0.4	719	1.74	36.8	
6	15	0.4	483	2.71	36.1	
7	15	0.8	917	1.47	36.9	
8	15	0.8	2080	1.70	38.4	
9	20	0.2	533	1.57	39.0	
10	20	0.2	466	1.48	39.6	1.12
11	20	0.4	846	1.56	40.6	1.13
12	20	0.4	895	1.61	40.1	
13	20	0.6	1201	1.40	41.2	1.11
14	20	0.6	1178	1.43	41.2	
15	20	0.8	1519	1.37	42.2	1.10
16	20	0.8	1502	1.39	42.0	1.09
17	20	1.0	1819	1.40	42.0	
18	20	1.0	1809	1.33	43.1	
19	20	1.2	2432	1.18	43.0	
20	20	1.2	2421	1.16	44.3	1.06
21	30	0.4	684	1.25	45.1	1.12
22	30	0.4	625	1.32	46.2	
23	30	0.8	1073	1.28	48.4	1.07
24	30	0.8	1103	1.28	47.9	
25	40	0.4	547	1.27	54.0	1.11
26	40	0.4	562	1.28	52.4	
27	40	0.8	832	1.26	53.1	1.10
28	40	0.8	973	1.25	54.1	
29	50	0.4	479	1.27	57.9	1.12
30	50	0.4	455	1.27	57.8	
31	50	0.8	737	1.27	58.6	1.11
32	50	0.8	774	1.27	60.2	
33	60	0.4	456	1.28	64.4	1.13
34	60	0.4	463	1.28	64.3	
35	60	0.8	669	1.28	65.3	1.11
36	60	0.8	654	1.27	65.7	
37	80	0.2	304	1.38	75.1	n.d.[a]
38	80	0.2	339	1.31	75.7	
39	80	0.4	432	1.28	77.0	1.15
40	80	0.4	397	1.32	74.4	
41	80	0.6	493	1.29	77.4	1.11
42	80	0.6	478	1.28	77.0	
43	80	0.8	541	1.31	77.5	1.11
44	80	0.8	587	1.29	78.3	1.11
45	80	1.0	661	1.29	79.3	
46	80	1.0	647	1.29	78.8	
47	80	1.2	969	1.25	80.6	
48	80	1.2	818	1.27	79.9	1.10
49	100	0.4	376	1.36	94.1	
50	100	0.4	387	1.42	95.1	1.16
51	100	0.8	512	1.28	95.9	1.12
52	100	0.8	498	1.28	96.8	

[a] *The applied technique for fixation of the pellets during the image analysis was compromised by the small pellet size, and consequently the aspect ratio could not be determined.*

Table 2: Coding of the influence variables for statistical evaluation

variable	level (Nm)	coded level	variable	level %(w/w)	coded level
ΔTq	0.2	-1	MCC	20	-1
ΔTq	0.4	-0.6	MCC	30	-0.75
ΔTq	0.6	-0.2	MCC	40	-0.5
ΔTq	0.8	+0.2	MCC	50	-0.25
ΔTq	1.0	+0.6	MCC	60	0
ΔTq	1.2	+1	MCC	80	+0.5
			MCC	100	+1

Evaluation of Runs With Less Than 20% (W/W) MCC

In all experiments with 10% (w/w) MCC, a lot of wall adhesion was observed, and the mass was seen to move irregularly. The large difference in the water content at the end of liquid addition between repeated experiments with 10% (w/w) MCC and a ΔTq of 0.4 N•m is assumed to derive from an inhomogeneous liquid distribution caused by the wall adhesion. During the drying phase, the adhered material became partly detached from the wall, and up to 25% of fines (<180 μm) were seen. The experiments with 15% (w/w) MCC showed less adhesion, but fine particles were formed during the drying phase. The appearance of fine particles can be explained by attrition of the formed agglomerates caused by the friction of the rotation plate. The experiments with 10% and 15% (w/w) MCC resulted in poor reproducibility and wide agglomerate size distribution, therefore (Table 1), and the agglomerates cannot be characterized as pellets. The process variables were not optimized for each formulation but were kept constant for all experiments. Thus, it might be possible to produce pellets with 10% or 15% (w/w) MCC if the process variables are optimized specifically for these formulations. Because of the low quality of the product, the results from the experiments with 10% and 15% (w/w) MCC are not discussed further or shown in any figures.

Evaluation of Runs Containing at Least 20% (w/w) MCC

All formulations with 20% (w/w) or more MCC produced pellets over a broad size range with good reproducibility as listed in Table 1. The results of the multiple linear regression analysis are summarized in Table 3.

Table 3: Full second order polynomials according to Eq. 1 for the different response variables: coefficient (standard error) *p-value* Bold: coefficients with p-values < 0.001, $r^2_{adj.}$:adjusted coefficient of determination

	Mean	MCC	ΔTq	MCC^2	ΔTq^2	MCCxΔTq	
Response variable	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	r^2_{adj}
Pellet size	590	-412	469	279	175	-406	0.977
d_{gw}	(22)	(19)	(21)	(33)	(35)	(28)	
	2.796E-26	2.449E-23	2.265E-23	2.720E-10	1.153E-05	5.266E-17	
Distribution	1.249	-0.007 (0.014)	-0.066	0.131	-0.006 (0.027)	0.072	0.598
s_g	(0.017)	0.628	(0.016)	(0.025)	0.809	(0.022)	
	1.037E-42		2.082E-04	7.363E-06		0.002	
Water content	64.9	26.2	1.91	3.59	-0.85	0.06	0.996
WC	(0.32)	(0.27)	(0.31)	(0.48)	(0.50)	(0.41)	
	0	0	2.615E-07	4.960E-09	0.100	0.881	
Aspect Ratio	1.109	0.019	-0.031	0.006	0.002	0.001	0.745
AR	(0.004)	(0.004)	(0.005)	(0.007)	(0.008)	(0.007)	
	1.545E-28	2.479E-04	2.606E-05	0.376	0.847	0.916	

The pellet size distribution was found to be wide (large s_g values) for formulations with 20% (w/w) MCC, except when using a ΔTq value of 1.2 N•m. From 30 to 100% (w/w) MCC, the s_g values were in the range between 1.25 and 1.42. A trend showing increasing ΔTq values leading to lower s_g values was found, which was confirmed by the multiple linear regression analysis (Table 3). The s_g values found in this investigation are slightly higher than those reported previously from experiments with similar formulations (4,13).

Image analysis of pellets from selected experiments with 20% (w/w) and more MCC gave rise to similar values of aspect ratio in the range from 1.06 to 1.16. However, the multiple linear regression analysis showed a significant decrease of aspect ratio with decreasing amount of MCC and increasing ΔTq, respectively.

The water content at the end point of liquid addition was significantly influenced by the fraction of MCC (linear and quadratic coefficient) and ΔTq (linear coefficient only). However, by far the most important term was the linear coefficient for MCC (Table 3). Thus, for fixed levels of ΔTq (0.4 and 0.8 N•m), simple linear regression was performed for water content and fraction of MCC. An increasing MCC content is seen to give rise to a higher water content (Figure 1).

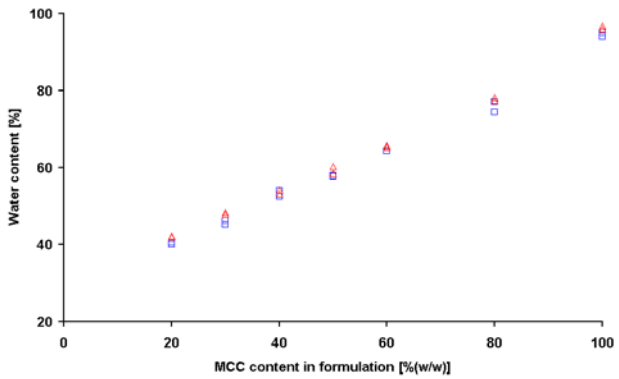

Figure 1: Correlation between the MCC content and the water content at the end of liquid addition for two torque increase values (ΔTq) (=0.4Nm, Δ=0.8Nm)

Once the moisture content in the mass has reached a certain level, agglomerate growth by coalescence will occur. Because of the ability of MCC to absorb water, increasing the MCC content in the mass will increase the water content needed for agglomerate growth to occur. This explains why increasing MCC

content gives rise to higher water content. Only a small increase in the water content is needed to increase the ΔTq value from 0.4 to 0.8 N•m, leading to values that are almost superimposed (Figure 1). The regression equations for the water content based on dry mass as a function of the MCC content for the 2 ΔTq values are shown in Table 4, together with regression equations found by other authors (16-20) using extrusion/spheronization. The coefficients of determination (r^2) indicate a linear correlation between the content of MCC and the amount of water needed for production of spherical pellets. Thoma and Ziegler (21) reported on a linear correlation between the water content based on wet mass and the fraction of MCC for 2 types of radial extruders. The slope of the straight line might depend on the nature of the MCC type used or the nature of the second component in the binary mixture. However, the type of pelletization equipment and the setting of the process variables may also influence the amount of water needed for successful pelletization. The shear stresses during the whole pelletization process can affect the necessary amount of granulation liquid. According to the "crystallite gel" model for MCC, higher shear stresses will result in higher amounts of water necessary during the process (20). This finding is supported by other studies (21,22).

Table 4: Correlations between the content of MCC (%(w/w)) in the formulation and the water content (based on dry mass) from binary mixtures. (Water content=slope x MCC + intercept)

Study	Formulation	Binary mixtures of	Slope	Intercept	r^2	95% conf. interval for the slope	n[a]
Current[b]	Rotary processor	MCC : Lactose	0.66	26.0	0.989	0.61 - 0.70	14
Current[c]	Rotary processor	MCC : Lactose	0.66	27.5	0.990	0.62 - 0.70	14
(16)	Sieve extrusion	MCC : Lactose	0.60	20.0	n.d.[d]	n.d.[d]	3
(17)	Ram extruder	MCC : Barium sulphate	0.79	17.6	0.968	0.63 - 0.96	7
(18)	Radial-screw-extruder	MCC : β-Cyclodextrin	0.90	25.3	0.969	0.67 - 1.12	6
(19)	Twin-screw-extruder	MCC : Lactose	1.35	19.1	0.996	1.27 - 1.43	8
(20)	Twin-screw-extruder	MCC : DCPD[e]	1.44	32.6	0.995	1.37 - 1.51	11

[a] *Number of data points*

[b] *Torque increase (ΔTq) =0.4N•m*

[c] *Torque increase (ΔTq) =0.8N•m*

[d] *Not determined - to few data points*

[e] *Dicalcium phosphate dihydrate*

The highest slopes were obtained by the use of a twin-screw extruder, whereas smaller slopes (Table 4) originate from a ram extruder, from sieving, or from a direct pelletization process in a rotary processor. The 95% confidence intervals for the slope show a significant difference for the results obtained from the twin-screw extruder compared to the other types of equipment (Table 4). This difference can be explained by the higher shear stresses acting on the excipients in a twin-screw extruder compared to other extruders and a rotary processor.

For the mean pellet size, all coefficients in the full second-order model were found to be significant (Table 3). Increasing amounts of MCC give rise to smaller pellets (Figure 2). Agglomerates containing MCC and water shrink during drying (19,23), and increasing amounts of MCC therefore lead to increased shrinkage and smaller agglomerates (20). This could explain why using the same ΔTq values and increasing the amount of MCC leads to a smaller pellet size (Figure 2). From Figure 2 it can also be seen that the small difference in the water content caused by increasing the ΔTq value from 0.4 to 0.8 N•m results in a large difference in the pellet size.

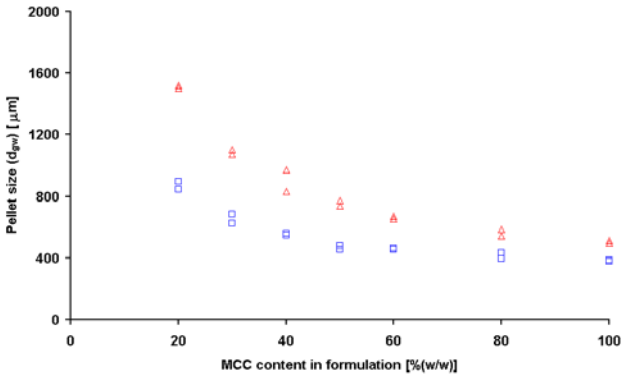

Figure 2: Correlation between the MCC content and the pellet size for two torque increase values (ΔTq) (=0.4Nm, Δ=0.8Nm)

Linear correlations were found between ΔTq and water content and ΔTq and pellet size for the formulations containing 20% and 80% (w/w) MCC. Increasing ΔTq values led to higher water content and larger pellet size for both formulations (Figures 3 and 4).

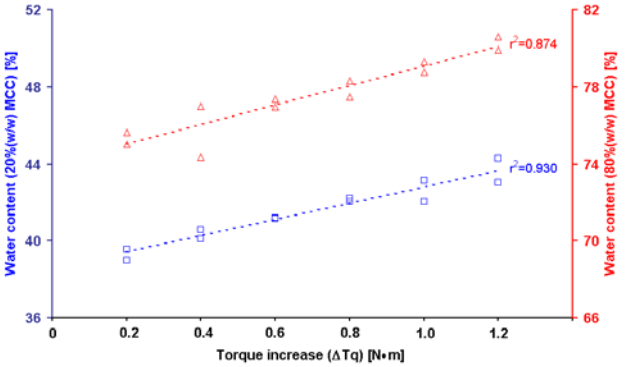

Figure 3: Correlation between the torque increase (ΔTq) and the water content at the end of liquid addition for two different formulations (=20%(w/w) MCC, Δ=80%(w/w) MCC)

These results concur with those published previously (5) using a 50% (w/w) MCC formulation. The increase in water content can be seen to be independent of the content of MCC. Therefore, when formulations containing MCC and lactose are pelletized in a rotary processor using torque measurements, a certain increase in ΔTq will give rise to the same increase in water content. However, this is not the case with the pellet size. The increase in d_{gw} can be seen to depend on the content of MCC. The same torque increase will lead to a larger pellet size when using low compared to high MCC contents. Again, this phenomenon can be explained by the shrinkage of the pellets during drying.

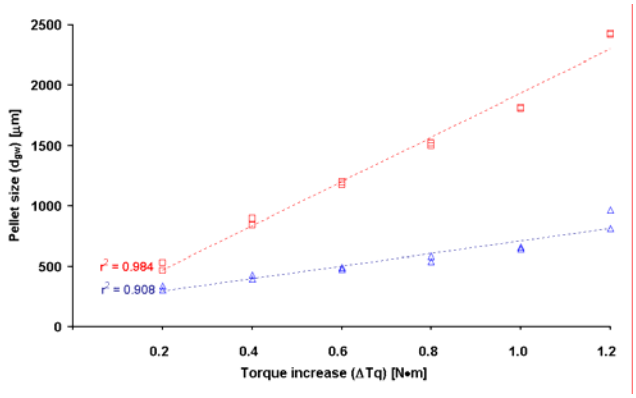

Figure 4: Correlation between the torque increase (ΔTq) and the pellet size for two different formulations (=20%(w/w) MCC, Δ=80%(w/w) MCC)

For the formulation with 20% (w/w) MCC, water content in the range of 39% to 44% gave rise to pellets with d_{gw} varying from approximately 500 to 2400 µm, showing how sensitive the process is to changes in the water content. The linear correlation between ΔTq and d_{gw}, however, shows that the pellet size can be controlled by torque measurement.

CONCLUSION

Spherical pellets of formulations of a broad range of MCC contents can be prepared in a reproducible way in a rotary processor using ΔTq as an end-point detection method. The ΔTq-controlled rotary processor is therefore a suitable tool for the development of new formulations. Increasing amounts of MCC have to be accompanied by an increase in ΔTq to produce pellets of the same size, and the suitable ΔTq value is therefore dependent on the MCC content.

By comparing the data of this investigation with results from the literature, it was found that generally a lower water content and a higher minimal amount

of MCC are needed to produce spherical pellets in a rotary processor compared to the extrusion/spheronization process, especially a twin-screw extruder. These results can be consistently explained by the crystallite-gel model for MCC.

Agglomerate growth by coalescence depends on the plasticity and deformability of the wet mass, ie, on the rheological properties of the mass. Because the torque of a rotating plate or impeller depends on the rheological properties of the mass, there is generally supposed to be a correlation between torque increase and agglomerate growth. The use of ΔTq for end-point control is assumed, therefore, to be also suitable for different formulations and for other types of fluidized bed rotor granulators, as well as mixer granulators.

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