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Torque rheological parameters to predict pellet quality in extrusion–spheronization☆

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Abstract

This study explored the feasibility of predicting the quality of microcrystalline cellulose (MCC) pellets prepared by extrusion–spheronization using torque rheological characterization. Rheological properties of eleven MCC grades as well as their binary mixtures with lactose (3:7) at various water contents were determined using a mixer torque rheometer (MTR). Derived torque parameters were: maximum torque and cumulative energy of mixing (CEM). CEM values of MCC powders ($CEM_{(MCC)}$) could be attributed to their physical properties such as crystallinity, $V_{low\ P}$ and V_{total} (volumes of mercury intruded in their pores at low pressure and the total intrusion volume), bulk and tapped densities. For both MCC powders and their binary mixtures, strong correlation was observed between their torque parameters and the properties of their pellets formed with 30 and 35% (w/w) water. Since this relationship was valid over a broad water content range, rheological assessment for pre-formulation purposes need not be performed at optimized water contents. These results demonstrated the usefulness of torque rheometry as an effective means of comparing and evaluating MCC grades especially when substitution of equivalent grades is encountered. In so doing, the tedious and expensive pre-production (pre-formulation and optimization) work can be considerably reduced.

Keywords: Torque rheometry; Pre-formulation; Extrusion–spheronization; Microcrystalline cellulose

1. Introduction

Extrusion–spheronization is the most widely used pelletization technique in the pharmaceutical industry as it is a robust and reproducible pellet production process. The vital excipient often associated with extrusion–spheronization is microcrystalline cellulose (MCC). It functions as a molecular sponge to absorb water and aid in the binding and lubrication of moistened powder mass during extrusion (Fielden et al., 1988; Heng and Koo, 2001; Liew et al., 2005). The extrudates are resilient yet brittle, allowing them to break up into even shorter extrudates, which are subsequently plasticized and rounded into spherical pellets with the aid of MCC.

As an excipient with many uses in the formulation of pharmaceutical products, a wide variety of commercial MCC grades with their respective claimed advantages are available. However, due to the differences in raw materials (including source origin, plant composition used and processing conditions during manufacture), variabilities in MCC batches and grades are inevitable and subsequently manifested in its physical characteristics. As it is extremely difficult to quantitate the overall influence of each property on the actual behavior of MCC in extrusion–spheronization using one-factor-at-a-time methods, pre-formulation tools to classify them into groups of equivalent performance or to predict their performance will be extremely useful. Recently, a pre-formulation tool based on artificial neural network (ANN) and data clustering was developed. It was able to classify eleven MCC grades into several groups based on their interaction with water (Soh et al., 2004). Additionally, the effects of MCC physical properties on their respective maximum torque ($Torque_{max}$) values were also discussed in that study.

Mixer torque rheometry (MTR) can be used to characterize the rheological properties or cohesiveness of moistened powder masses during mixing. MTR monitors simultaneously the changes occurring in a powder mass with different binder concentration, mixing time and speed of the mixer blades. These

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changes vary proportionately to the resistance experienced by the mixer blades, which are in turn, reflected as torque changes.

Several investigators (Hancock et al., 1991, 1992; Landin et al., 1994; Rowe, 1996; Parker et al., 1991) have employed the results obtained from torque measurements to relate to changes that occur during wet massing and study binder–substrate interactions. They had also investigated the effects of instrument design, mixing kinetics, shaft speed and sample weight on the torque generated and thereby, the properties of the wet mass in question.

Johansen et al. (1999) used the MTR to determine the properties of melt agglomerates while Chatlapalli and Rohera (1998) characterized the cohesiveness of diltiazem hydrochloride/cellulose mixes. Although Rowe and Sadeghnejad (1987) studied the rheological requirements of microcrystalline/water mixes and showed differences between the MCC grades, it was not extended to illustrate the impact of this variation to other pharmaceutical processes such as tabletting and pelletization. In fact, limited work has been carried out to evaluate the usefulness of torque measurements in predicting the performance of a wide range of commercially available MCC grades in the process of making spherical pellets.

In this current work, another torque parameter, cumulative energy of mixing (CEM), was proposed. It could track and reveal changes in the effects of MCC physical properties on the rheological behavior of its moistened masses as water content was increased. Additionally, torque rheological properties of MCC–lactose binary mixtures (3:7) would also be determined and their respective $\text{Torque}_{\text{max(blend)}}$ and $\text{CEM}_{\text{(blend)}}$ values derived. This formulation was chosen because it is commonly used for pellet manufacture by extrusion–spheronization.

Thereafter, this report will demonstrate the feasibility of using $\text{Torque}_{\text{max(blend)}}$, $\text{CEM}_{\text{(MCC)}}$ and $\text{CEM}_{\text{(blend)}}$ values of MCC grades to predict the quality of their resultant pellets which would in turn, reflect the performance of different MCC grades in extrusion–spheronization. It is believed that this pre-formulation tool can help to assess the likelihood of potential production problems that may arise with grade or supplier substitution. It can also aid in the selection of equivalent alternatives to an existing inventory, resulting in more prudent utilization of available resources.

For clarity, the maximum torque values of MCC powder and MCC–lactose binary mixtures would be referred to as $\text{Torque}_{\text{max(MCC)}}$, $\text{Torque}_{\text{max(blend)}}$ whereas their respective CEM values would be referred to as $\text{CEM}_{\text{(MCC)}}$ and $\text{CEM}_{\text{(blend)}}$ hereinafter.

2. Materials and methods

2.1. Materials

A total of eleven MCC grades were used in this study. They were: Emcocel 50M, Prosolv 50M (Mendell, NJ, USA), Pharmacel 101 and Pharmacel 102 (DMV, Veghel, The Netherlands), Celex 101 (ISP, NJ, USA), Viva Pur 101 (J. Rettenmaier & Sohne, Holzmulle, Germany), Avicel PH 101, Avicel PH 102, Avicel PH 301, Avicel PH 302 and Ceolus KG 801 (Asahi,

Table 1
Physical properties of MCC grades

MCC grade	$(d(v)_{50})$ (µm)	X_{cr} (%)	ρ_b (g ml^{-1})	ρ_t (g ml^{-1})	ρ_{true} (g ml^{-1})	$V_{low\ P}$ (ml g^{-1})	$V_{high\ P}$ (ml g^{-1})	V_{total} (ml g^{-1})	ε (%)	$W_{710\,\mu m}$	W_s
Avicel PH 101	76.53	69.56	0.31	0.43	1.559	1.19	0.35	1.54	65.45	36.10	4.46
	(0.53)	(0.95)	(0.003)	(0.003)	(0.003)	(0.03)	(0.01)	(0.03)	(2.46)	(0.33)	(0.30)
Avicel PH 102	132.81	69.49	0.31	0.42	1.561	1.22	0.44	1.67	66.92	36.12	4.24
	(1.95)	(0.29)	(0.002)	(0.002)	(0.005)	(0.06)	(0.04)	(0.09)	(5.61)	(0.34)	(0.12)
Avicel PH 301	73.55	76.37	0.43	0.56	1.557	0.86	0.29	1.14	61.15	30.27	3.87
	(0.54)	(7.98)	(0.004)	(0.004)	(0.000)	(0.06)	(0.02)	(0.07)	(2.88)	(0.24)	(0.08)
Avicel PH 302	139.41	84.81	0.46	0.59	1.557	0.75	0.30	1.06	60.11	29.82	3.98
	(1.36)	(6.99)	(0.003)	(0.003)	(0.011)	(0.06)	(0.03)	(0.08)	(2.76)	(0.85)	(0.31)
Ceolus KG 801	66.65	78.61	0.19	0.30	1.558	2.04	0.57	2.61	76.95	37.17	4.73
	(0.39)	(8.89)	(0.002)	(0.001)	(0.000)	(0.05)	(0.02)	(0.07)	(2.55)	(0.75)	(0.24)
Celex 101	57.18	72.93	0.28	0.40	1.561	1.38	0.45	1.83	68.28	38.79	4.90
	(0.16)	(7.28)	(0.003)	(0.001)	(0.006)	(0.02)	(0.03)	(0.01)	(1.16)	(1.05)	(0.40)
Emcocel 50M	70.86	70.38	0.27	0.38	1.550	1.30	0.36	1.66	65.72	38.10	5.07
	(0.21)	(1.64)	(0.003)	(0.001)	(0.018)	(0.02)	(0.01)	(0.01)	(0.33)	(0.29)	(0.15)
Prosolv 50M	81.44	70.73	0.30	0.41	1.572	1.45	0.35	1.81	70.00	38.25	5.20
	(0.54)	(1.60)	(0.003)	(0.001)	(0.001)	(0.03)	(0.05)	(0.05)	(1.16)	(1.01)	(0.39)
Viva Pur 101	68.04	73.52	0.32	0.45	1.554	1.22	0.30	1.52	65.35	36.53	4.63
	(0.25)	(3.23)	(0.002)	(0.001)	(0.000)	(0.07)	(0.01)	(0.08)	(1.93)	(0.83)	(0.02)
Pharmacel 101	62.24	72.37	0.30	0.44	1.554	1.11	0.49	1.60	62.29	37.64	4.84
	(0.22)	(2.53)	(0.001)	(0.001)	(0.002)	(0.10)	(0.02)	(0.11)	(0.86)	(0.92)	(0.10)
Pharmacel 102	143.44	73.08	0.34	0.44	1.548	1.22	0.23	1.52	61.55	37.50	4.65
	(0.66)	(4.14)	(0.003)	(0.002)	(0.002)	(0.04)	(0.04)	(0.07)	(3.60)	(0.62)	(0.04)

Values in parentheses represent the standard deviations.

Osaka, Japan). Prosolv 50M is a silified grade of MCC and is physically equivalent to Emcocel 50M. All MCCs were of the same batch as those quoted previously (Heng and Koo, 2001).

Two kilogram of MCC and lactose (Pharmatose 200M, DMV, Veghel, The Netherlands) mixtures in the ratio of (3:7) were pre-mixed using geometric dilution followed by mixing in a double cone mixer (AR 40, Erweka, Germany) at 40 rpm for 1 h. Distilled water was the granulation liquid used.

2.2. Methods

2.2.1. Physical characterization of MCC powders

Mean particle size ($d(v)_{50}$), bulk (ρ_b) and tapped (ρ_t) densities, % crystallinity (X_{cr}), micromeritic parameters ($V_{low\ P}$, $V_{high\ P}$, V_{total} and ε) and extrusion–spheronization parameters ($W_{710\ \mu m}$ and W_s) were previously determined for all MCCs (Heng and Koo, 2001) and reproduced in Table 1 for ease of reference. $V_{low\ P}$ and $V_{high\ P}$ refer to the amount of mercury intruded into the pores at low and high pressure, respectively, while V_{total} is the sum of $V_{low\ P}$ and $V_{high\ P}$ and refers to the total volume of mercury intruded into the pores. ε denotes the percent porosity. $W_{710\ \mu m}$ and W_s refer to the predicted water requirement for preparing pellets with a mean size of 710 µm and the spheronization water sensitivity of MCC, respectively.

True densities (ρ_{true}) of all the MCC grades were determined using a helium pycnometer (Penta-Pycnometer, Quantachrome Instruments, USA) and presented in Table 1. The MCC powders were pre-dried in a convection oven at 105 °C and cooled in a dessicator before use. Large sample cells were filled to 90% with the dry MCC powders and purged with helium gas for 10 min before actual analysis commenced. Analysis was performed in triplicates and results averaged.

The theoretical amount of water required to achieve capillary state of liquid saturation in the MCC powders, $\%H_2O_{(cap)}$ (Table 2) was estimated from their true and tapped densities according to Eq. (3) below. MCC bulk powder referred to the bulk powder mass (MCC particles and air spaces):

$$\text{Volume occupied by 1 g of MCC particle (cm}^3) = x \quad (1)$$

$$\text{Volume occupied by 1 g of MCC bulk powder (cm}^3) = y \quad (2)$$

$$\text{Volume available for added water to reside per unit g of MCC powder} = (y - x) \quad (3)$$

where $x = 1/\rho_{true}$ and $y = 1/\rho_t$.

2.2.2. MTR measurements (torque rheological properties)

$Torque_{max(MCC)}$, $Torque_{max(blend)}$ values (Table 2) and the rheological properties of MCC grades with increasing water contents and mixing times were determined according to methods previously reported (Soh et al., 2004). For the MCC powders, 15 g of powders were used for every run. Their $CEM_{(MCC)}$ values at eight different added water contents ranging from 75 to 175% (w/w) were calculated (Table 3a) by integrating the areas under the measured torque versus mixing time curves (Figs. 1 and 2).

$CEM_{(blend)}$ values (Table 3b) were determined for the MCC–lactose binary mixtures in the same way although the water contents tested ranged from 25 to 55% (w/w) and the amount of material used was higher at 25 g. Due to the high proportion of soluble lactose present in the binary mixtures, the

Table 2
$Torque_{max(MCC)}$, $Torque_{max(blend)}$, $\%H_2O_{(max\ T)}$ and $\%H_2O_{(cap)}$ values for MCC grades

MCC grade	$Torque_{max(MCC)}$ (Nm)[a]	$Torque_{max(blend)}$ (Nm)	$\%H_2O_{(max\ T)}$ (%, w/w)[a]	$\%H_2O_{(cap)}$ (%, w/w)[b]
Avicel PH 101	1.129	0.657	135	167.3
	(0.006)	(0.065)	(0)	
Avicel PH 102	0.938	0.838	135	196.9
	(0.045)	(0.012)	(15)	
Avicel PH 301	2.017	1.447	95	114.0
	(0.027)	(0.094)	(9)	
Avicel PH 302	1.847	1.338	95	105.5
	(0.100)	(0.023)	(9)	
Ceolus KG 801	0.973	0.909	150	272.5
	(0.109)	(0.025)	(0)	
Celex 101	0.999	0.928	140	187.8
	(0.047)	(0.081)	(9)	
Emcocel 50M	0.934	0.878	140	200.7
	(0.053)	(0.116)	(9)	
Prosolv 50M	0.928	0.886	145	182.7
	(0.014)	(0.132)	(9)	
Viva Pur 101	0.824	0.507	130	159.4
	(0.089)	(0.001)	(9)	
Pharmacel 101	0.846	0.674	140	164.0
	(0.055)	(0.015)	(9)	
Pharmacel 102	0.912	0.586	130	162.2
	(0.044)	(0.078)	(9)	

Values in parentheses represent the standard deviations.
[a] Taken from (Soh et al., 2004).
[b] Calculated from mean values of ρ_{true} and ρ_t.

Table 3a
Cumulative energies of mixing ($CEM_{(MCC)}$) values for MCC grades at different added water contents

Added water content (%, w/w)	Avicel PH 101	Avicel PH 102	Avicel PH 301	Avicel PH 302	Ceolus KG 801	Celex 101	Emcocel 50M	Prosolv 50M	Viva Pur 101	Pharmacel 101	Pharmacel 102
75	3.183	3.120	12.208	8.472	4.038	4.495	3.352	5.202	3.606	3.550	3.943
	(0.571)	(0.189)	(5.122)	(0.802)	(0.496)	(0.282)	(0.332)	(1.183)	(0.335)	(0.506)	(0.131)
90	3.358	7.154	58.843	32.285	5.235	4.490	3.734	3.929	5.584	4.309	4.762
	(0.506)	(1.234)	(14.922)	(0.846)	(0.442)	(0.193)	(0.433)	(0.996)	(1.021)	(0.276)	(0.043)
100	6.033	9.797	89.777	82.840	7.707	9.097	9.652	9.247	13.635	15.217	13.955
	(0.511)	(1.304)	(0.274)	(2.696)	(1.359)	(1.593)	(2.511)	(1.425)	(1.587)	(1.842)	(2.107)
110	9.019	14.665	21.806	48.118	15.589	13.261	12.65	10.466	16.022	21.549	20.077
	(1.646)	(4.423)	(0.615)	(7.013)	(2.124)	(0.652)	(2.144)	(0.964)	(2.270)	(4.468)	(6.490)
125	18.056	39.230	19.438	44.334	49.866	43.658	19.833	19.972	46.247	46.448	56.491
	(0.409)	(6.000)	(0.615)	(5.908)	(7.297)	(2.562)	(1.722)	(1.072)	(6.632)	(2.073)	(3.025)
130	31.115	59.749	2.863	2.325	56.059	67.166	40.172	40.270	53.549	61.164	60.255
	(1.583)	(3.878)	(0.515)	(0.582)	(3.957)	(8.949)	(2.177)	(4.049)	(2.504)	(2.247)	(8.587)
150	63.998	31.139	1.468	1.783	32.502	47.269	31.514	40.428	23.109	22.264	30.308
	(3.212)	(3.290)	(0.091)	(0.202)	(3.877)	(3.749)	(5.484)	(3.435)	(0.878)	(0.105)	(1.742)
175	5.740	1.252	1.043	1.488	19.368	17.114	8.513	1.405	0.959	1.122	2.233
	(1.208)	(0.165)	(0.248)	(0.476)	(1.747)	(1.576)	(1.241)	(0.135)	(0.139)	(0.105)	(0.836)

Values in parentheses represent the standard deviations.

Table 3b
Cumulative energies of mixing ($CEM_{(blend)}$) values of MCC–lactose binary mixtures (3:7) at different added water contents

Added water content (%, w/w)	Avicel PH 101	Avicel PH 102	Avicel PH 301	Avicel PH 302	Ceolus KG 801	Celex 101	Emcocel 50M	Prosolv 50M	Viva Pur 101	Pharmacel 101	Pharmacel 102
25	7.897	8.620	24.873	26.338	11.673	9.756	10.423	9.850	9.253	10.416	9.291
	(0.133)	(0.053)	(2.510)	(1.921)	(0.235)	(0.689)	(0.345)	(0.248)	(0.798)	(0.983)	(0.845)
30	10.969	9.875	37.803	41.013	13.954	11.992	13.268	13.398	11.607	14.448	14.639
	(0.167)	(0.036)	(3.422)	(2.281)	(0.257)	(1.129)	(0.211)	(0.254)	(0.895)	(1.198)	(1.109)
35	12.195	16.242	69.337	57.250	18.921	19.250	15.189	16.550	15.084	18.552	18.455
	(2.235)	(1.330)	(0.135)	(1.997)	(0.687)	(0.370)	(0.628)	(0.256)	(0.745)	(0.479)	(1.876)
40	17.714	21.716	43.267	41.975	28.271	27.712	19.283	22.256	22.252	28.105	20.871
	(0.287)	(0.037)	(7.705)	(0.625)	(0.807)	(2.525)	(0.225)	(1.334)	(2.843)	(1.026)	(0.199)
45	18.483	18.243	7.386	1.166	39.694	28.344	23.595	28.236	17.136	27.729	23.204
	(0.830)	(2.756)	(0.888)	(0.092)	(0.211)	(1.949)	(1.678)	(0.262)	(2.041)	(0.597)	(1.669)
50	2.571	1.836	0.893	0.893	39.106	2.506	20.631	0.514	1.943	0.645	1.612
	(0.040)	(0.032)	(0.020)	(0.002)	(0.352)	(0.036)	(0.543)	(0.003)	(0.134)	(0.060)	(0.211)

Values in parentheses represent the standard deviations.

propensity of these powder mixtures to be overwetted is correspondingly increased. Consequently, a reduced water content range and larger powder mass were needed to ensure that torque responses generated for the MCC–lactose binary mixtures were adequate for quantification and differentiation between various mixtures. Triplicates were performed for each MCC grade for every added water content tested (Fig. 3).

2.2.3. Pellet manufacture and characterization

Pellets were previously prepared using 3:7 blends of MCC and lactose with added water contents of 25, 30, 35, 40 and 45% (w/w) in an spheronizer (Model 120, Caleva Process Solutions, UK). They were subsequently characterized for flow, friability, bulk and tapped densities. Pellets were not prepared at water contents greater than 50% (w/w) because lump formation was prevalent due to overwetting. Methods and results for pellet preparation and characterization have been previously reported (Heng and Koo, 2001) and would not be re-elaborated. However, these results were used for correlation analysis in this study to establish the relationship between the derived torque parameters and pellet properties.

2.2.4. Data analysis

2.2.4.1. Normalization of values. All readings for torque parameters and pellet properties were normalized using the following equation prior to correlation analyses:

$$X_{\text{nor}} = \frac{X_i - X_{\text{min}}}{X_{\text{max}} - X_{\text{min}}} \tag{4}$$

where X_{nor} is the normalized X value while X_i refers to the actual value being transformed. X_{max} and X_{min} are the maximum and minimum values of each torque parameter, respectively.

2.2.4.2. Correlation analysis. CEM and $\text{Torque}_{\text{max}}$ values of the MCC powders and their binary mixtures ($\text{CEM}_{\text{(MCC)}}$, $\text{CEM}_{\text{(blend)}}$, $\text{Torque}_{\text{max(MCC)}}$ and $\text{Torque}_{\text{max(blend)}}$) were correlated to the physical properties (Tables 4 and 5) of MCC grades and their respective pellets (Pearson's correlation analysis, SPSS Version 13.0 for Windows, SPSS Inc., IL, USA). It should be mentioned that the effects of MCC physical properties on their maximum torques generated ($\text{Torque}_{\text{max(MCC)}}$) was reported in our earlier study (Soh et al., 2004).

3. Results and discussion

3.1. Theoretical water content requirement at capillary stage of liquid saturation

Based on their estimated $\%H_2O_{\text{(cap)}}$ values, the eleven MCCs could be broadly divided into three groups: low, intermediate and high. The two high density MCCs, Avicel PH 301 and PH 302 belonged to the "low" group since they needed only small amounts of added water to achieve capillary stage (approximately 110%, w/w). On the other hand, Ceolus KG 801, the most porous MCC grade was placed in the "high" group as it was able to accommodate much larger quantities of water before the internal and interstitial spaces were completely filled (approximately 270%, w/w). The remaining eight MCCs could accommodate 160–200% (w/w) of water before complete saturation and were placed in the "intermediate" group.

In the earlier work (Soh et al., 2004), saturation water:MCC ratio which represented the added water content needed to achieve the maximum torque (will be referred to as $\%H_2O_{\text{(max T)}}$ hereinafter) and $\text{Torque}_{\text{max(MCC)}}$ values for each MCC were reported. For ease of comparison, these values were reproduced in Table 2. To elucidate the effects of MCCs physical properties on the CEM values, it is imperative to first establish the relationship between $\%H_2O_{\text{(cap)}}$, $\text{Torque}_{\text{max(MCC)}}$ and the $\%H_2O_{\text{(max T)}}$.

From Table 2, it was clear that $\%H_2O_{\text{(max T)}}$ was distinctly lower than the corresponding $\%H_2O_{\text{(cap)}}$ for the respective MCCs. This was because the maximum torque did not occur at the capillary state but rather, between the capillary and the funicular states. Based on the proposed states of liquid saturation by Newitt and Conway-Jones (1958), the funicular state is one where the moisture present in the inter-particulate spaces coalesces to form a continuous network of liquid interspersed with air whereas the capillary state is reached when all the void spaces within the moistened powder mass (also referred to as granulate) are completely filled with liquid (Augsburger and Vuppala, 1997). Thus, relatively dry particles in the funicular state are not sufficiently bound together to form a cohesive mass which would provide enough resistance to the mixer blades during wet massing in the MTR (measured torque < $\text{Torque}_{\text{max(MCC)}}$). Conversely, surface water associated with the cohesive granulate (capillary state) served to lubricate and facilitate remodeling of the granulate during mixing (measured torque < $\text{Torque}_{\text{max(MCC)}}$). Therefore, the maximum resistance to the mixer blades during wet massing in the MTR arose when the moistened MCC particles are between the funicular and the capillary states of liquid saturation.

Another noteworthy point was the relative difference between $\%H_2O_{\text{(cap)}}$ and $\%H_2O_{\text{(max T)}}$. For some MCCs (particularly the ones in the 'low' group), this difference was relatively small compared to that for Ceolus KG 801 ($\%H_2O_{\text{(cap)}}$: 272%, w/w; $\%H_2O_{\text{(max T)}}$: 150%, w/w). This observation could be explained in terms of the sensitivity of the moistened mass to increasing added water contents. For Avicel PH 301 and PH 302, the consistencies of their moistened masses were very sensitive to changes in added water content as was reflected in the sharp peaks obtained on the 2D plot of measured torque versus water:MCC ratio (Soh et al., 2004). On the contrary, the corresponding plot for Ceolus KG 801 exhibited a broad plateau (with a small peak), suggesting that the added water could be accommodated in the large inter-particulate spaces within its bulk powder mass without marked changes in its consistency. Consequently, a much larger difference was observed between its $\%H_2O_{\text{(cap)}}$ and $\%H_2O_{\text{(max T)}}$ values.

3.2. Effect of MCC physical properties

3.2.1. On cumulative energies of mixing for MCC powders, $\text{CEM}_{\text{(MCC)}}$

Strong links were established between $\text{CEM}_{\text{(MCC)}}$ values, physical properties (% crystallinity, $V_{\text{low P}}$, V_{total}, ε, bulk and

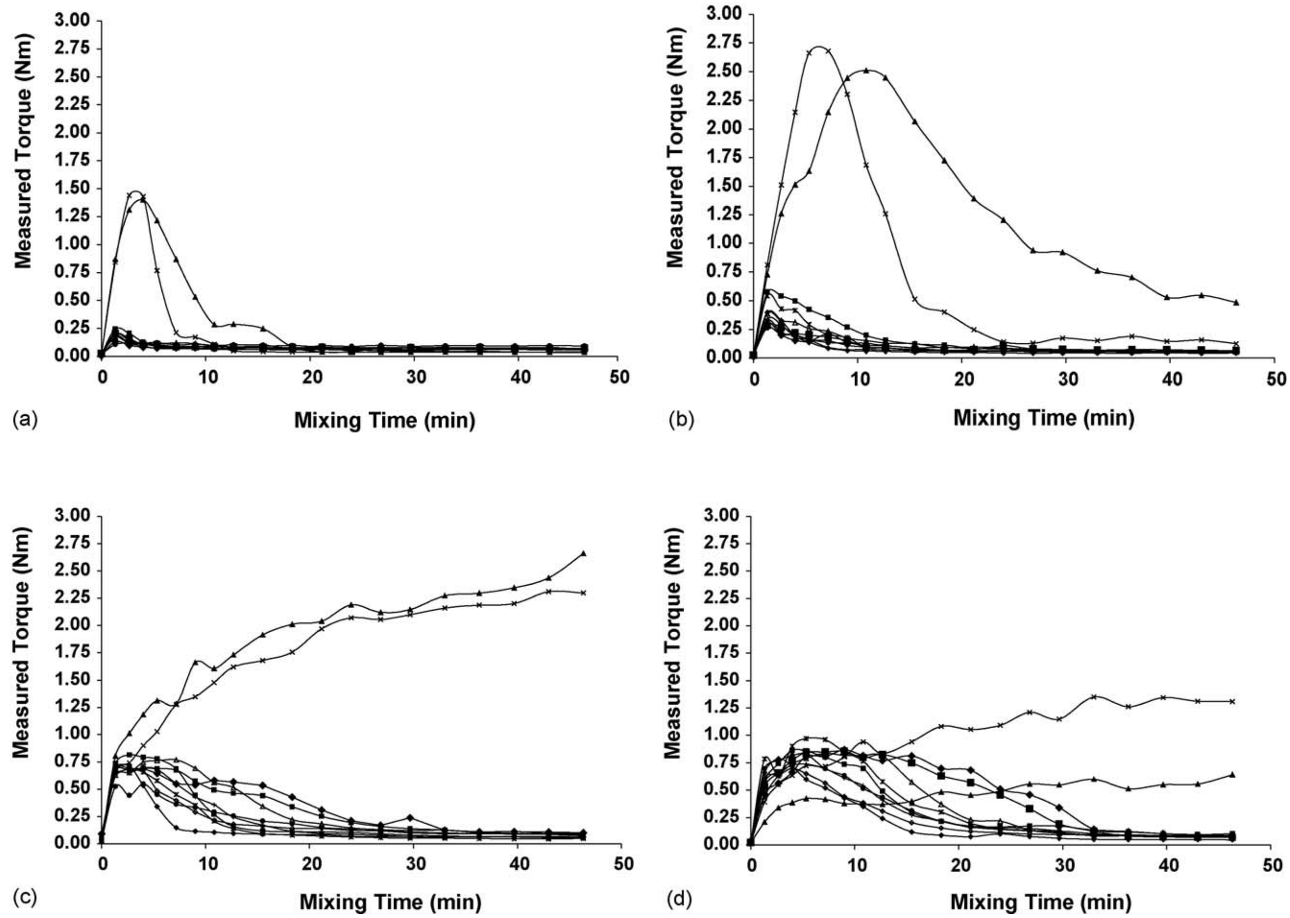

Fig. 1. Variation of measured torque with mixing time for (◆) Avicel PH 101, (■) Avicel PH 102, (▲) Avicel PH 301, (×) Avicel PH 302, (✳) Ceolus KG 801, (✸) Celex 101, (+) Emcocel 50M, (◇) Prosolv 50M, (△) Viva Pur 101, (⧫) Pharmacel 101 and (■) Pharmacel 102 with (a) 75% (w/w), (b) 90% (w/w), (c) 100% (w/w) and d) 110% (w/w) of added water.

Table 4a
Pearson's correlation coefficient, r, of $CEM_{(MCC)}$ values at different added water contents with physical properties of MCC grades[a,b]

Added water content (%, w/w)	Physical properties of MCC grade (powder)								
	X_{cr}	$V_{low\ P}$	$V_{high\ P}$	V_{total}	ε	ρ_b	ρ_t	$W_{710\ \mu m}$	W_s
MCC powder									
75	–	–	–	–	–	0.755** (0.007)	0.743** (0.009)	−0.844** (0.001)	−0.653* (0.030)
90	–	–	–	–	–	0.775** (0.005)	0.771** (0.005)	−0.899** (0.000)	−0.776** (0.005)
100	0.709* (0.015)	−0.686* (0.020)	–	−0.677* (0.022)	–	0.867** (0.001)	0.866** (0.001)	−0.952** (0.000)	−0.777** (0.005)
110	0.856** (0.001)	–	–	–	–	0.716* (0.013)	0.723* (0.012)	−0.746** (0.008)	–
125	–	–	–	–	–	–	–	–	–
130	–	0.604* (0.049)	–	0.630* (0.038)	–	−0.765** (0.006)	−0.748** (0.008)	0.876** (0.000)	0.637* (0.035)
150	−0.672* (0.024)	–	–	–	–	−0.639* (0.034)	−0.655* (0.029)	0.722* (0.012)	–
175	–	0.728* (0.011)	0.655* (0.029)	0.752** (0.008)	0.720* (0.012)	−0.661* (0.027)	−0.665* (0.025)	–	–

* Significant correlation at the 95% level of confidence (two-tailed).
** Significant correlation at the 99% level of confidence (two-tailed).
[a] Values in parentheses represent the probabilities.
[b] No correlation for $(d(v)_{50})$ and ρ_{true} at all added water contents.

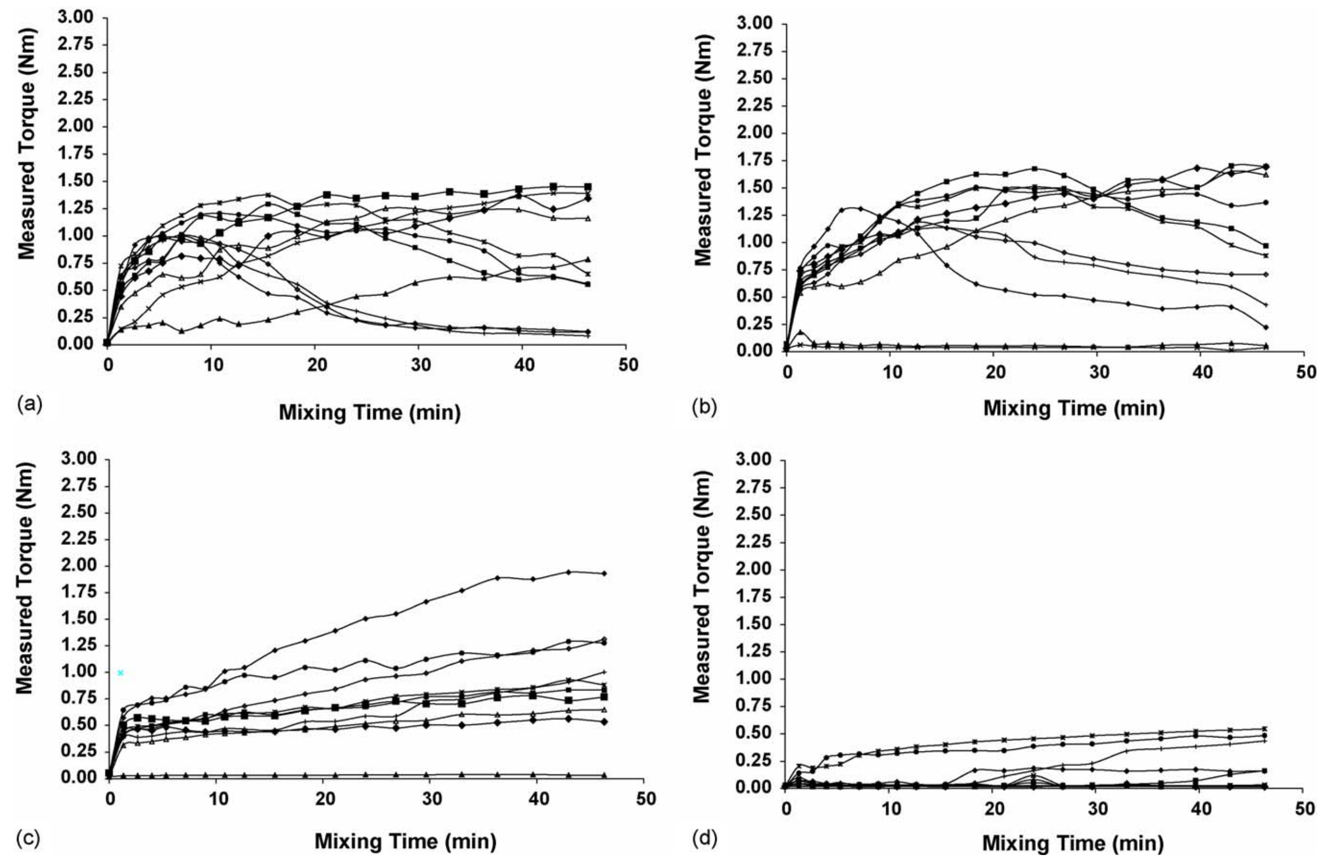

Fig. 2. Variation of measured torque with mixing time for (◆) Avicel PH 101, (■) Avicel PH 102, (▲) Avicel PH 301, (×) Avicel PH 302, (✳) Ceolus KG 801, (✸) Celex 101, (+) Emcocel 50M, (◊) Prosolv 50M, (△) Viva Pur 101, (⧫) Pharmacel 101 and (■) Pharmacel 102 with (a) 125% (w/w), (b) 130% (w/w) (c) 150% (w/w) and (d) 175% (w/w) of added water.

tapped densities) and $W_{710\,\mu m}$ and W_s of the MCC grades (Table 4a). An interesting observation was the reversal in correlation at higher added water contents (>125%, w/w). For instance, at low added water contents (<125%, w/w), % crystallinity, bulk and tapped densities were positively correlated to the $CEM_{(MCC)}$ values while $V_{low\,P}$ and V_{total} were negatively correlated. This meant that at low added water contents, denser and more crystalline MCCs with low porosities tended to generate larger torques and thus required more energy for granulation. Therefore, MCC grades that were denser produced correspondingly denser masses and required more energy to shear. Similarly, more crystalline MCC powders contributed to much less plastic deformation, thereby increasing the total energy of mixing. However at higher added water contents (>125%, w/w), crys-

Table 4b
Pearson's correlation coefficient, r, of $CEM_{(blend)}$ values at different added water contents with physical properties of MCC grades[a,b]

Added water content (%, w/w)	Physical properties of MCC grade (powder)								
	X_{cr}	$V_{low\,P}$	$V_{high\,P}$	V_{total}	ε	ρ_b	ρ_t	$W_{710\,\mu m}$	W_s
MCC–lactose mixtures									
25	0.800** (0.003)	–	–	–	–	0.7878** (0.004)	0.783** (0.004)	−0.928** (0.000)	−0.714* (0.014)
30	0.655** (0.011)	−0.585* (0.028)	–	−0.600* (0.023)	–	0.794** (0.001)	0.733** (0.003)	−0.916 (0.000)	−0.717* (0.013)
35	0.570* (0.033)	−0.580* (0.030)	–	−0.588* (0.027)	–	0.785** (0.001)	0.733** (0.003)	−0.914** (0.000)	0.765** (0.006)
40	0.719** (0.004)	–	–	–	–	0.601* (0.023)	0.578* (0.03)	−0.796** (0.001)	0.616* (0.043)
45	–	0.884 (0.000)	0.668** (0.009)	0.909** (0.000)	0.775* (0.001)	−0.922** (0.000)	−0.837* (0.000)	0.819** (0.000)	0.788** (0.004)

* Significant correlation at the 95% level of confidence (two-tailed).
** Significant correlation at the 99% level of confidence (two-tailed).
[a] Values in parentheses represent the probabilities.
[b] No correlation for $(d(v)_{50})$ and ρ_{true} at all added water contents.

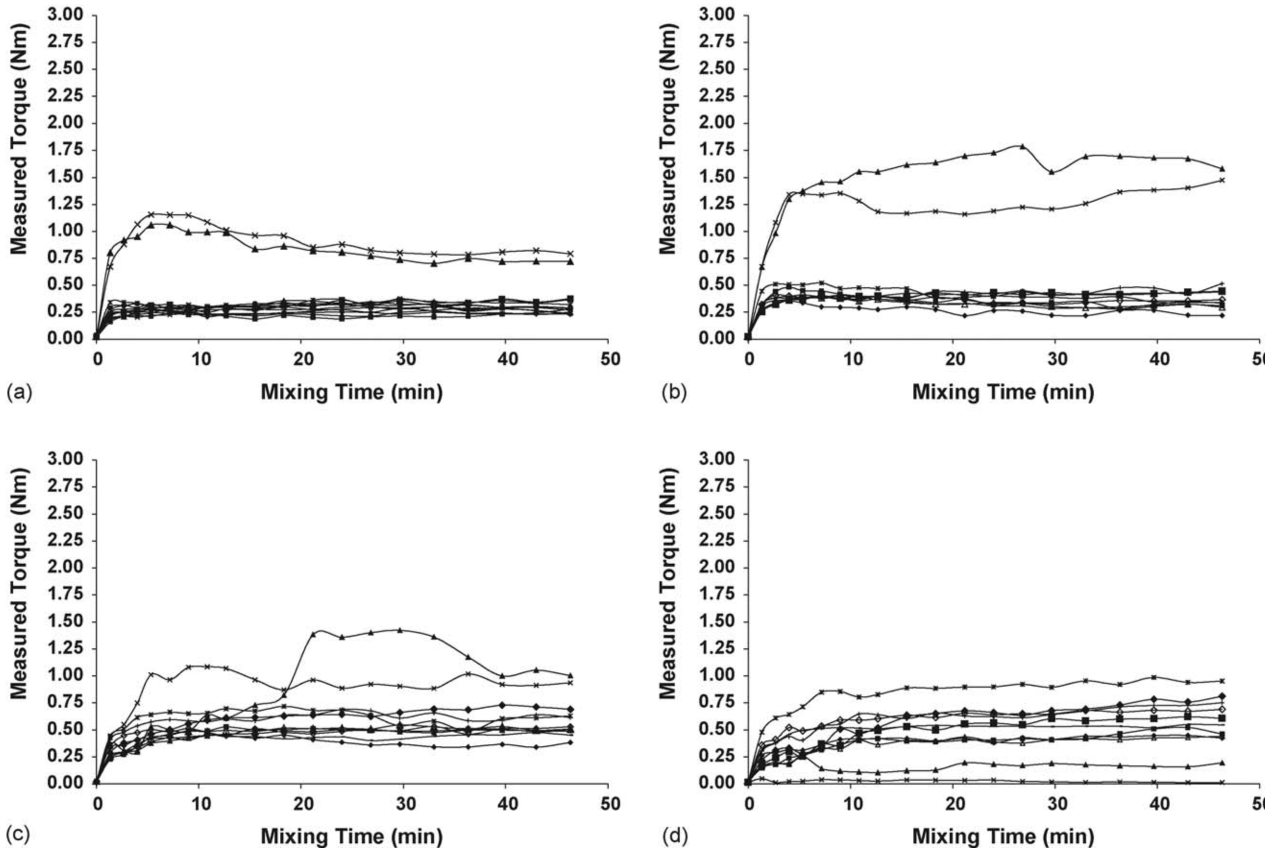

Fig. 3. Variation of measured torque with mixing time for MCC–lactose binary mixtures (3:7) of (◆) Avicel PH 101, (■) Avicel PH 102, (▲) Avicel PH 301, (×) Avicel PH 302, (✳) Ceolus KG 801, (✹) Celex 101, (+) Emcocel 50M, (◇) Prosolv 50M, (△) Viva Pur 101, (⧫) Pharmacel 101 and (■) Pharmacel 102 with (a) 30% (w/w), (b) 35% (w/w) (c) 40% (w/w) and (d) 45% (w/w) of added water.

Table 5a
Pearson's correlation coefficient, r, of $CEM_{(MCC)}$ values at different added water contents with pellet properties[a,b]

Added water content (%, w/w)	Pellet strength	Pellet properties							
		Flow		Friability index		Bulk density		Tapped density	
		Water content (%, w/w)		Water content (%, w/w)		Water content (%, w/w)		Water content (%, w/w)	
		30	35	30	35	30	35	30	35
75	0.914** (0.000)	−0.859** (0.001)	−0.869** (0.001)	0.836** (0.001)	0.643* (0.033)	0.748** (0.008)	0.704* (0.016)	0.697* (0.017)	–
90	0.930** (0.000)	−0.896** (0.000)	−0.861** (0.001)	0.894** (0.000)	0.658* (0.028)	0.793** (0.004)	0.778** (0.005)	0.738* (0.010)	–
100	0.992** (0.000)	−0.943** (0.000)	−0.947** (0.001)	0.901** (0.000)	0.642* (0.033)	0.818** (0.002)	0.751** (0.008)	0.777** (0.005)	–
110	0.754** (0.007)	−0.687** (0.020)	−0.768** (0.006)	0.624* (0.040)	–	–	–	–	–
125	–	–	–	–	–	–	–	–	–
130	−0.891** (0.000)	0.892** (0.000)	0.873** (0.000)	−0.851** (0.000)	−0.676* (0.022)	−0.893** (0.000)	−0.721* (0.012)	−0.877** (0.000)	–
150	−0.758** (0.007)	0.768** (0.006)	0.784** (0.004)	−0.616* (0.044)	–	–	–	–	–
175	–	–	–	–	–	–	–	–	–

* Significant correlation at the 95% level of confidence (two-tailed).
** Significant correlation at the 99% level of confidence (two-tailed).
[a] Values in parentheses represent the probabilities.
[b] No correlation for $(d(v)_{50})$ and ρ_{true} at all added water contents.

Table 5b
Pearson's correlation coefficient, r, of $CEM_{(blend)}$ values at different added water contents with pellet properties[a,b]

Added water content (%, w/w)	Pellet strength	Pellet properties							
		Flow		Friability index		Bulk density		Tapped density	
		Water content (%, w/w)		Water content (%, w/w)		Water content (%, w/w)		Water content (%, w/w)	
		30	35	30	35	30	35	30	35
25	0.988**	−0.910**	−0.961**	−0.897**	0.707*	0.821**	0.739**	0.787**	–
	(0.000)	(0.000)	(0.000)	(0.000)	(0.015)	(0.002)	(0.009)	(0.004)	
30	0.988**	−0.925**	−0.958**	0.879**	0.647*	0.799**	0.722**	0.760**	–
	(0.000)	(0.000)	(0.000)	(0.000)	(0.032)	(0.012)	(0.012)	(0.007)	
35	0.978**	−0.912**	−0.924**	0.902**	0.671*	0.793**	0.764**	0.742**	–
	(0.000)	(0.000)	(0.000)	(0.000)	(0.024)	(0.004)	(0.006)	(0.009)	
40	0.914**	−0.769**	−0.846**	0.828**	0.672*	0.679*	0.730**	0.635*	–
	(0.000)	(0.006)	(0.001)	(0.002)	(0.024)	(0.022)	(0.011)	(0.026)	
45	−0.790**	0.840**	0.772**	−0.734**	–	−0.767**	–	−0.767**	–
	(0.004)	(0.001)	(0.005)	(0.010)		(0.006)		(0.006)	

* Significant correlation at the 95% level of confidence (two-tailed).
** Significant correlation at the 99% level of confidence (two-tailed).
[a] Values in parentheses represent the probabilities.
[b] No correlation for $(d(v)_{50})$ and ρ_{true} at all added water contents.

tallinity, bulk and tapped densities became negatively correlated to the $CEM_{(MCC)}$ while $V_{low\ P}$ and V_{total} were positively correlated.

The above findings explained the behavior of MCC particles in terms of liquid saturation. Very low water contents (75–90%, w/w) corresponded to the pendular stage of liquid saturation for most of the MCCs whereby the powder particles were only loosely held together by "surface tension at the solid–liquid–air interface and the hydrostatic suction pressure of the liquid bridge" (Augsburger and Vuppala, 1997). These granulates were weak and easily deformed under the shear forces imparted by the mixer blades. Thus, $CEM_{(MCC)}$ values were mainly affected by the bulk and tapped densities. Denser MCCs required more energy for mixing (Table 3a).

With the exception of Avicel PH 301 and PH 302, an increase in the added water content led to a corresponding progression in liquid saturation to the funicular state where the MCC particles were held together by thick, lens-like rings of water. Once again, powder densities exerted dominant influences on the CEM values but the effects of crystallinity and pore volumes also began to manifest. As crystalline powders were less readily deformed, more energy had to be expended during wet massing; hence the positive correlation observed between $CEM_{(MCC)}$ (at 100–110%, w/w, water) and crystallinity. On the other hand, granulates of the more porous MCC grades were still in the comparatively dry stage (funicular or pre-funicular) and were readily broken down during wet massing. Hence, more porous MCC grades were associated with lower $CEM_{(MCC)}$ values at these moisture levels.

As the added water content increased (from 125 to 150%, w/w), the void spaces within the granulates of the remaining MCCs began to saturate (pre-capillary). For most of the MCCs in the "intermediate" group, their $Torque_{max(MCC)}$ values occurred within this water content range. At this point, formation of liquid bridges between particles in the granulates was enhanced and their intra-particle bonds strengthened, making the granulates stronger and less deformable by the shear forces exerted. This led to marked increases in their $CEM_{(MCC)}$ values (Table 3a). However at this moisture range, the two high density MCCs would have been overwetted (droplet state) to generate any appreciable torques; hence, the observed reversal in correlation at water contents beyond 125% (w/w). While most of the MCC grades were either overwetted or maximally saturated, Ceolus KG 801 (most porous grade) was still able to accommodate more water even when 175% (w/w) of water was already added. Consequently, strong correlation was still seen despite high water contents.

Another noteworthy point was the lack of correlation between $CEM_{(MCC)}$ values at 125% (w/w) and all the physical properties evaluated. From Fig. 2a and Table 3a, it was clear that all the MCC grades generated appreciable torque values and their $CEM_{(MCC)}$ values were not markedly different from each other, including those of the high-density grades. As a result, the effects of MCC physical properties could not be amply exemplified. Slight increase in the added water content to 130% (w/w) resulted in overwetting for the high density grades, leading to a drastic drop in their $CEM_{(MCC)}$ values and the observed correlation results in Table 4a.

$CEM_{(MCC)}$ values at most added water contents were also significantly related to $W_{710\,\mu m}$ and W_s. The sign of correlation was also reversed beyond the water content of 125% (w/w). At low water levels, MCC grades with lower water requirements during extrusion–spheronization tended to generate higher torques. These MCC grades also tended to be denser, more crystalline and less porous as concluded from the earlier correlation between these physical properties shown in Table 4a. Therefore, the influence of $W_{710\,\mu m}$ and W_s could be explained in the same manner as above.

Table 6
Pearson's correlation coefficient, r, of $Torque_{max(MCC)}$ and $Torque_{max(blend)}$ with pellet properties[a,b]

	Pellet strength	Friability index		Pellet flow		Bulk density		Tapped density	
		Water content (%, w/w)		Water content (%, w/w)		Water content (%, w/w)		Water content (%, w/w)	
		30	35	30	35	30	35	30	35
$Torque_{max(MCC)}$	0.974**	0.948**	0.747**	−0.906**	−0.904**	0.865**	0.835**	0.816**	0.611*
	(0.000)	(0.000)	(0.008)	(0.000)	(0.000)	(0.001)	(0.001)	(0.002)	(0.046)
$Torque_{max(blend)}$	0.869**	0.821**	0.763**	−0.749**	−0.854**	0.729*	0.676*	0.701*	0.442
	(0.001)	(0.002)	(0.006)	(0.008)	(0.001)	(0.011)	(0.022)	(0.016)	(0.174)

* Significant correlation at the 95% level of confidence (two-tailed).
** Significant correlation at the 99% level of confidence (two-tailed).
[a] No correlation between $Torque_{max}$ and the physical properties of pellets prepared with 40% and 45% (w/w) of water.
[b] Values in parentheses represent the probabilities.

3.2.2. On cumulative energies of mixing for MCC–lactose binary mixtures, CEM(blend)

In general, the trend of correlation between cumulative energies of mixing and MCC physical properties was not affected by the presence of lactose. This meant that the effects of MCC physical properties on the $CEM_{(blend)}$ values were comparable to those on the $CEM_{(MCC)}$ as discussed in the preceding section. Furthermore, a similar reversal in correlation was also observed albeit at a different water content (>40%, w/w). These observations were not unexpected because consistencies of the moistened powder masses, as reflected in their torque responses, were mainly governed by the MCC component within the binary mixture. MCC's ability to control the movement and distribution of water within moistened powder masses has been well documented (Fielden et al., 1988; Heng and Koo, 2001; Liew et al., 2005). This regulation of water availability in turn, governs the rheological properties of the moistened mass.

Compared to the MCC powders, the reversal in correlation between cumulative energies of mixing at higher water contents and MCC physical properties was less critical. This was because the optimum water contents for pellet production do not usually exceed 40% (w/w) since the tendency of overgrowth (lump formation) is correspondingly increased at higher water contents.

3.3. Relationship between torque parameters and pellet properties

In general, good correlations were observed between the torque parameters (cumulative energies of mixing and maximum torque) and the properties of pellets prepared at 30 and 35% (w/w) water (Tables 4 and 5). At water contents greater than 40% (w/w), pellets prepared with the two high density MCC grades, Avicel PH 301 and PH 302, were too large for flow and density determinations using the orifice flow and tapping methods, respectively. Furthermore, friability indices of all MCC pellets were not significantly different (ANOVA, $p > 0.05$) at high water contents because the amount of added water was sufficient to form strong pellets after drying that could withstand the abrasive forces in the friability test.

At lower water contents, i.e. <125% (w/w) (for MCC powders) and <45% (w/w) (for MCC–lactose binary mixtures), MCC grades that required less energy for mixing tended to yield pellets which were weaker, more friable, less dense but flowed better (Table 5). Beyond these water contents, the relationship between CEM values and pellet properties were reversed although it would be reiterated that higher water contents were comparatively less common for pelletization by extrusion–spheronization.

Strong links (Table 6) were also established between maximum torque values of both MCC powders, their binary mixtures ($Torque_{max(MCC)}$ and $Torque_{max(blend)}$) and the physical properties of their pellets formed at 30 and 35% (w/w) of water (ANOVA, $p < 0.01$). These correlation results showed that MCC grades or their blends, which generated higher $Torque_{max}$ values tended to produce pellets that were stronger, denser and less friable. However, these pellets exhibited poorer flowability. A higher torque value indicated that the moistened masses were less amenable to remodeling. Therefore, their resultant pellets were comparatively less round and had compromised flowability. MCC grades with higher bulk and tapped densities were found to generate larger torques at saturation (Soh et al., 2004). As a result, it could be inferred that denser MCCs produced denser and less friable pellets. This inference corroborated with the earlier report (Heng and Koo, 2001) where the authors concluded that MCC grades, which possessed lower water retentive capacities, in turn, produced denser pellets with poorer flow properties.

Collating the correlation results obtained thus far, several important insights could be drawn. Firstly, physical properties of pellets prepared by different MCC grades could be readily assessed and compared from the torque rheological parameters of MCC powders alone instead of characterizing their binary mixtures. This eliminated the extra step of preparing powder blends containing MCC when a rapid comparison between MCC grades is needed during the pre-formulation stage. Also, this indicated that the spheronization process was largely governed by MCC.

Secondly, the relationship between torque parameters and pellet properties extend over a broad range of water contents. This meant that the choice of water content for rheological characterization of MCC grades would not affect the prediction and comparison of their pellet properties critically. Consequently, the need to optimize water content for rheological studies during the pre-formulation phase would also be minimized.

Furthermore, as torque responses result from the summative effects and interactions between different MCC physical properties, derived torque parameters for the respective MCC grades would represent a given MCC grade more comprehensively than a single physical attribute. Given the ease and rapidity of determining both torque parameters, preliminary evaluation of a given MCC grade for wet granulation applications would be considerably expedited.

4. Conclusion

Findings from this study have demonstrated the usefulness of torque rheometry as a simple, reliable and competent pre-formulation tool to predict the quality of MCC pellets prepared by extrusion–spheronization. Particularly in events where new MCC grades are encountered or considered as potential candidates for substituting existing grades, a simple torque rheological characterization might suffice. This can complement and reduce the laborious and expensive pre-formulation and optimization studies, which are traditionally performed when new excipients are encountered.

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