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Research Article

Evaluation of the Physicochemical Properties and Compaction Behavior of Melt Granules Produced in Microwave-Induced and Conventional Melt Granulation in a Single Pot High Shear Processor

Z. H. Loh,[1] B. Y. Sia,[1] Paul W. S. Heng,[1] C. C. Lee,[2] and Celine V. Liew[1,3]

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Abstract. Recently, microwave-induced melt granulation was shown to be a promising alternative to conventional melt granulation with improved process monitoring capabilities. This study aimed to compare the physicochemical and compaction properties of granules produced from microwave-induced and conventional melt granulation. Powder admixtures comprising equivalent proportions by weight of lactose 200 M and anhydrous dicalcium phosphate were granulated with polyethylene glycol 3350 under the influence of microwave-induced and conventional heating in a 10-L single pot high shear processor. The properties of the granules and compacts produced from the two processes were compared. Relative to conventional melt granulation, the rates at which the irradiated powders heated up in microwave-induced melt granulation were lower. Agglomerate growth proceeded at a slower rate, and this necessitated longer massing durations for growth induction. These factors prompted greater evaporative moisture losses from the melt granules. Additionally, nonuniform heating of the powders under the influence of microwaves led to increased inter-batch variations in the binder contents of resultant melt granules and a reliance of content homogeneity on massing duration. Agglomerate growth proceeded more rapidly under the influence of conventional heating due to the enhanced heating capabilities of the powders. Melt granules produced using the conventional method possessed higher moisture contents and improved content homogeneity. The compaction behavior of melt granules were affected by their mean sizes, porosities, flow properties, binder, and moisture contents. The last two factors were responsible for the disparities in compaction behavior of melt granules produced from microwave-induced and conventional melt granulation.

KEY WORDS: compaction; compressibility; high shear granulation; melt granulation; microwave.

INTRODUCTION

Melt or thermoplastic granulation is a technique of agglomerating fine particles by the use of a meltable binder material which is solid at room temperature but softens or melts at elevated temperatures. Unlike binding liquids which are removed via drying after wet granulation, the meltable binder material remains as a constituent in the end product, rendering melt granulation an ideal method for agglomeration studies (1). Despite rising interests in the use of microwave technology for drying pharmaceutical materials and products, the use of microwaves as an alternative source of energy for granulation, *e.g.*, melt granulation remains largely unexplored. This stemmed from the paucity of information available on the dielectric properties of regular pharmaceutical materials in their dry states. Dielectric properties are fundamental electrical characteristics of materials which govern their behavior when subjected to microwaves for purposes of heating, drying, material processing as well as process monitoring (2,3). For microwave-induced melt granulation (MMG) to be viable, knowledge of the dielectric properties of pharmaceutical materials is essential as material dielectric responses control the efficiency and extent to which microwave energy can be effectively coupled into the material for heat production and binder activation.

In a previous study (4), MMG was demonstrated and compared with conventional melt granulation (CMG), both of which were performed in a 10-L single pot high shear processor (UltimaPro™10, Collette NV, Wommelgem, Belgium). The processor is equipped with a thermoregulated mixer bowl and magnetron device capable of generating microwaves ranging from 0 to 900 W in power output. Equivalent proportions by weight of lactose 200 M and anhydrous dicalcium phosphate (DCP), both employed in concentrations of 41.7% (*w/w*), were granulated with 16.7% (*w/w*) polyethylene glycol 3350 under the influence of either microwave-induced heating or conventional heat energy that was derived from the thermoregulated mixer bowl set at 60°C. The effects of the different modes of heating and massing time on the heating capabilities of the powders as well as subsequent agglomerate growth were investigated.

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[1] GEA-NUS Pharmaceutical Processing Research Laboratory, Department of Pharmacy, Faculty of Science, National University of Singapore, 18 Science Drive 4, Singapore, 117543, Singapore.

[2] Akzo Nobel Surface Chemistry Pte. Ltd., 41 Science Park Road #03-03, The Gemini, Singapore Science Park II, Singapore, 117610, Singapore.

[3] To whom correspondence should be addressed. (e-mail: phalcv@nus.edu.sg)

In MMG, it was observed that the powders possessed low heat acquisition rates. Based on subsequent experimentation, this was found to be attributed primarily to the intrinsically poor dielectric response of the powder mixture that hampered effective material-microwave coupling necessary for heat production. Lactose 200 M and DCP possessed different dielectric responses with the latter being capable of absorbing microwaves to a greater extent. Therefore, to fully maximize the benefits of microwave-induced heating, higher concentrations of DCP would have been preferential. Furthermore, as air does not absorb microwaves, the heat that was generated in the air-powder mixture during massing was nonuniform in MMG as evidenced by the considerable inter-batch variations observed in the product temperatures measured on-line. Longer durations of massing were required for binder activation and agglomerate growth in MMG as a result of the low heat acquisition rates and nonuniform heating of the powders. Conversely, the nondiscriminating nature of thermal energy derived from the mixer bowl in CMG improved the efficiencies and uniformities at which the air-powder mixtures heated up during processing. This shortened processing times and resulted in greater inter-batch consistencies in product temperatures. Accordingly, product temperature was shown to be a more reliable indicator of agglomerate growth in CMG as compared with MMG.

In general, one of the primary purposes of granulation is to ensure content homogeneity in the final product. For melt granulation, content homogeneity is affected, firstly, by the heating capabilities of the powders under the combined influences of frictional heat arising from the shearing action of the impeller and the externally applied source of energy. This is followed by the subsequent distribution of binder material, in the form of molten droplets, throughout the agglomerating powder masses. Binder distribution can critically affect resultant granule properties. Based on this information, it was hypothesized that the different heating strategies employed in MMG and CMG would influence the distribution of molten binder during granulation which would in turn, affect the eventual physicochemical properties of the resultant melt granules.

The work previously published (4) focused on comparing the heating capabilities of the powders in MMG and CMG and how they influenced agglomerate growth and process monitoring. As an extension, the present study aimed to evaluate and compare the physicochemical properties and compaction behavior of melt granules produced from MMG and CMG. The binder distribution patterns, moisture contents, flow properties, and porosities of melt granules produced from MMG and CMG were first examined. Subsequently, the compaction behavior of the melt granules were investigated by compacting the granules under constant pressure and analyzing the porosities and mechanical strengths of the compacts formed. In view of the complex interplay among the properties of melt granules and their compacts, principal component analysis was employed to elucidate these inter-variable relationships. Specifically, the influences of the various physicochemical properties of melt granules produced in the two processes on the porosities and mechanical strengths of the corresponding compacts were examined. The compressibilities of selected batches of melt granules were also evaluated using the Heckel equation.

MATERIALS AND METHODS

Materials

The starting materials employed for melt granulation have been reported in reference (4). Analytical grade chloroform (Merck, Darmstadt, Germany) was used for the analyses of the binder contents of the melt granules. For moisture determination using the Karl Fischer method, Hydranal® Composite-2 (Riedel-de Haën, Seelze, Germany) was employed as the titrant. The working solvent comprised anhydrous methanol (Panreac Quimica S.A., Barcelona, Spain) and formamide (Hydranal® Formamid dry, Riedel-de Haën). Magnesium stearate (Riedel-de Haën) was used as a lubricant for studies on the compaction behavior and compressibility of melt granules.

Methods

Granulation

The methods by which MMG and CMG were performed in a 10-L single pot high shear processor have been reported in (4) and will not be re-elaborated in detail. To summarize, powder admixtures comprising equivalent proportions by weight of DCP and lactose 200 M were granulated with polyethylene glycol 3350 in the single pot high shear processor under the influence of microwave-induced and conventional heating. The granulation procedure employed for the two processes were identical with the following exceptions:

1. The microwave energy employed in MMG was substituted by heat derived from the mixer bowl maintained at 60°C in CMG.
2. A shorter range of massing time (6–12 min) was investigated for CMG as opposed to MMG (10–18 min) due to the disparities in heating capabilities of the powders and agglomerate growth propensities between the two processes.

All granulation runs were replicated at least thrice.

Yield and Size Analyses of Melt Granules

The methods by which the yield and size distribution of melt granules were determined have been reported (4) and will not be re-elaborated.

Binder Contents of Melt Granules

Based on an established method (5), the binder contents of melt granules were determined using a near-infrared spectrophotometer (UV-3600 Spectrophotometer, Shimadzu, Kyoto, Japan). Following size analyses, an accurately weighed quantity of melt granules was obtained from each sieved fraction and dispersed in a known volume of chloroform. Chloroform dissolves polyethylene glycol and thus served as an extracting agent for the binder material in the melt granules. Coarser granules of $\geq$1.00 mm were first dispersed in chloroform then ultrasonicated in a water bath for 30 s to improve extraction efficiency. The remnant granule materials, lactose 200 M and DCP, being insoluble in chloroform, were removed by membrane filtration (regenerated cellulose, 0.45 μm, Sartorius, Göttingen, Germany). The filtrate obtained was analyzed for its content of polyethylene glycol 3350 at 2,488 nm. Preliminary experiments performed on physical mixtures of the three formulation constituents showed minimal interferences from both lactose and DCP on the absorbance measurements of polyethylene glycol 3350 at the wavelength of interest. Three replicated experiments were carried out each time and the results averaged.

Moisture Contents of Melt Granules

The moisture contents of melt granules were determined using a Karl Fischer apparatus (701 KF Titrino, Metrohm Ion Analysis, Herisau, Switzerland). Representative samples (~25 g) of melt granules were obtained from each product batch and milled for 8 s using a small laboratory grinder. Coarser granules were subjected to an additional 5 s of milling. An accurately weighed quantity (~0.5 g) of milled granules was then introduced to the working solvent comprising a 1:1 ratio of anhydrous methanol and formamide. Prior to its use, the solvent was subjected to a pre-titration step for the removal of traces of residual moisture. This ensured that subsequent volumes of Karl Fischer reagent dispensed during the actual titration were attributed to moisture present in the milled granules *per se*. Three replicated experiments were carried out each time, and the results averaged.

Flow Properties of Melt Granules

The bulk densities of melt granules were determined by allowing them to flow freely with the aid of a glass funnel, into a graduated cylinder cut exactly at the 100-ml mark. The weight of granules occupying a volume of 100 ml was determined. Bulk density was calculated by dividing the weight of granules by its volume. The granules were then subjected to tapping (Stamfpvolumeter Stav 2003, JEL, Ludwigshafen, Germany) until they have attained a constant volume. Tapped density was calculated by dividing the weight of granules by its final, unchanged volume after tapping. Hausner ratios and compressibility indices of the granules were calculated from the following formulae (6):

$$\text{Hausner ratio} = \text{Tapped density}/\text{Bulk density}$$

$$\text{Compressibility index (\%)} = [(\text{Tapped density} - \text{Bulk density})/\text{Tapped density}] \times 100$$

A minimum of three replicated experiments was carried out each time and the results averaged.

True Densities of Melt Granules

Estimations of true density were performed on the melt granules that were previously milled. Prior to the test, the milled granules from each product batch were spread thinly on trays and dried overnight at 50°C in a vacuum oven set at 550 mbar (Gallenkamp, Loughborough, UK). Upon cooling, the dried, milled granules were packed into the measurement cells for true density estimations under helium purge (Pentapycnometer, Quantachrome, Boynton Beach, FL). Five replicated measurements were performed each time.

Porosities of Melt Granules

The porosities of melt granules were estimated from their tapped and true densities according to the following formula (7):

$$\text{Granule porosity (\%)} = [1 - -(\text{Tapped density}/\text{True density})] \times 100$$

Compaction of Melt Granules

A universal testing machine (Autograph AG-100kNE, Shimadzu) equipped with a 10-mm diameter flat-faced punch and die set was used for the compaction of melt granules. The melt granules were first dry mixed with 1% (*w*/*w*) magnesium stearate as a lubricant. An accurately weighed 0.5-g sample of the lubricated granules was transferred to the die cavity and compacted under a fixed pressure of 102 MPa. The rate of compaction was set at 5 mm/min. Compacts formed were gently ejected from the die and allowed to recover in an enclosed chamber for a minimum of 24 h prior to characterization. Eight compacts were prepared each time.

Mechanical Strengths and Porosities of Compacts

The mechanical strengths and porosities of the compacts formed were used to describe the compaction behavior of the melt granules. Upon recovery, all the compacts formed were accurately weighed using a three-decimal place electronic balance (CP423S, Sartorius). Thickness measurements were performed with a micrometer screw gauge (Mitutoyo, Kawasaki, Japan) at five predefined locations of each compact after recovery and averaged to obtain the mean thickness of the compact. Compact porosity was estimated using the following formula (8):

$$\text{Compact porosity (\%)} = (1 - d) \times 100$$

where d refers to the relative density of the compact calculated from the ratio of its apparent density (quotient of compact weight and volume) to the true density of its constituent melt granules as estimated earlier. The mechanical strengths of compacts were assessed using a hardness tester (HT1, Sotax, Allschwil, Switzerland). The average force (N) required to crush five compacts was determined.

Compressibility of Melt Granules

The compressibility of selected batches of melt granules, namely, melt granules prepared at 6 and 10 min in CMG as well as 18 min in MMG were also evaluated. An identical procedure as described above was applied, with the exception that both the die wall and lower punch were pre-lubricated with an alcoholic suspension of magnesium stearate prior to granule filling. The die and punches were cleaned and re-lubricated after each compaction cycle. Eight compacts were prepared at each of the compaction pressures of 13, 25, 38, 51, 63, 102, 152, 203, 253, and 304 MPa. The change in density of the granule bed as a function of the applied pressure was plotted and analyzed off-line using the Heckel equation (9):

$$\ln\left(\frac{1}{1-D}\right) = kP + A$$

where D refers to the relative density of the compact formed at a particular pressure P (MPa) and is calculated from the ratio of its apparent density (quotient of compact weight and volume) to the true density of its constituent melt granules. k and A are constants derived from the linear portion of the Heckel plot. k refers to the slope of the best fit line obtained from linear regression and its reciprocal represents the yield pressure of melt granules. Yield pressure provides a measure of the degree of plasticity and compressibility of the granules.

Multivariate Data Analysis

Principal component analysis (The Unscrambler®, version 9.8, Camo Inc., Bangalore, India) was performed to compare the relative influences of the various physicochemical properties of melt granules on their compaction behavior. The melt granulation experiments constituted the samples, whereas the variables included the mean size, span, % fines, bulk, and tapped densities, Hausner ratios, compressibility indices, porosities, moisture, and binder contents of melt granules as well as the mechanical strengths and porosities of resultant compacts formed under a fixed compaction pressure of 102 MPa. Upon entering the variables and samples, the software generated an output known as a loadings plot. The loadings plot provides a projection view of the inter-variable relationships among the parameters of interest (10).

RESULTS AND DISCUSSION

Yield and Size Distribution of Melt Granules

As useful reference to the present discussion, the yield and size distribution of melt granules as previously reported (4) are reproduced in Table I. To reiterate, increased massing times in both CMG and MMG enhanced the propensities for agglomerate growth, as evidenced by the increase in mean granule size with time and a generally low proportion of fines (<1%). Agglomerate growth, however, proceeded at a faster rate in CMG due to the higher heating rates of the powders. Optimal granule yields with desirable physical properties may thus be achieved within comparatively shorter process times (6–12 min) in CMG as compared with MMG where longer massing durations (10–18 min) were necessary for the production of reasonable yields of melt granules of comparable quality. Clearly, the range of massing times most optimal for agglomeration differed between MMG and CMG. The binder distribution patterns, moisture contents, flow properties, porosities, and compaction behavior of melt granules produced from MMG and CMG under optimal durations of massing were evaluated and compared as follows.

Binder Contents of Melt Granules

Binder content was defined as the proportion by weight (% *w*/*w*) of polyethylene glycol 3350 in the melt granules. The binder contents of the different size fractions of granules in CMG and MMG are shown in Figs. 1 and 2, respectively. Each data point in the bar chart represented the binder content of a particular size fraction of melt granules produced at a specific massing time and its corresponding error bar reflected the inter-batch variation in the binder content of granules of that particular size. Figs. 1 and 2 also provide information on the uniformity of binder distribution among the different size fractions of granules produced at the massing times investigated in CMG and MMG.

Theoretically, the binder constituted a proportion of 16.7% by weight of melt granules. At all massing times, it could be observed that the binder contents of the different granule fractions in both CMG and MMG closely approximated 16.7% (*w*/*w*) and decreased slightly as the sizes of granules fell below 355 μm. It could be observed at the outset that the binder was distributed more uniformly among the different size fractions of granules in CMG (Fig. 1) as compared with MMG (Fig. 2). Although a specific fraction of granules (180–250 μm) prepared at a massing time of 10 min in CMG possessed an unexpectedly high amount of binder, relatively consistent binder content values were achieved across all remaining size fractions of melt granules regardless of massing time. The small error bars further indicated that the inter-batch variations in binder contents of granules were minimal. These results provided evidence of a robust and reproducible melt granulation process under the influence of conventional heating.

Table I. Yield and Size Distribution of Melt Granules Produced in MMG and CMG

Process	Massing time (min)	Yield[a] (%)	Lumps[a] (%)	Fines[a] (%)	D_{50}[b] (μm)	Span[a]	Usable[a] (%)
MMG	10	97.73 (0.85)	0.64 (0.49)	0.86 (1.12)	473.8	0.96 (0.22)	97.10 (0.44)
	14	96.99 (1.37)	2.38 (1.60)	0.50 (0.53)	668.8	0.85 (0.17)	94.69 (2.33)
	16	78.15 (8.85)	32.67 (8.35)	0.05 (0.05)	1,666.7	0.97 (0.05)	52.13 (0.56)
	18	87.21 (13.08)	18.17 (23.70)	0.53 (0.62)	1,115.8	0.88 (0.12)	72.91 (27.08)
CMG	6	96.76 (0.33)	0.72 (0.12)	0.58 (0.08)	450.0	1.01 (0.01)	96.06 (0.38)
	8	94.94 (2.06)	1.58 (0.99)	0.28 (0.08)	619.2	0.94 (0.01)	93.43 (1.21)
	10	95.41 (1.36)	6.14 (4.20)	0.25 (0.20)	770.0	1.03 (0.04)	89.59 (5.14)
	12	87.73 (4.74)	28.63 (11.93)	0.20 (0.07)	1,436.7	1.01 (0.06)	62.82 (12.35)

Table reproduced from reference (4)

[a] Standard deviations are indicated in the parentheses

[b] D_{50} refers to the mass median diameter of melt granules

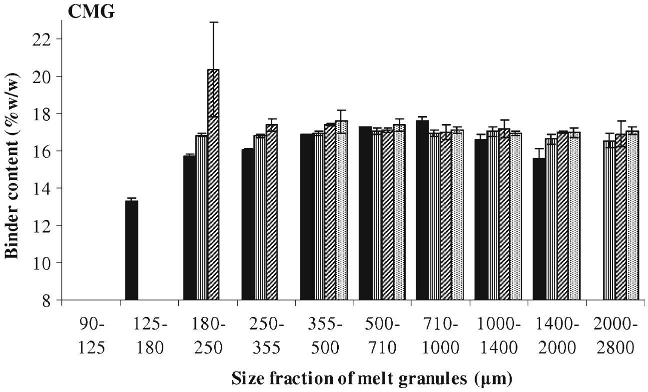

Fig. 1. Binder contents of the different size fractions of melt granules produced in CMG at massing times of 6 (■), 8 (▥), 10 (▨), and 12 min (░)

The situation was slightly different in MMG (Fig. 2). In spite of the longer durations of massing (10–18 min), it appeared that the binder material was distributed less homogeneously as could be inferred from the greater disparities in binder contents among the different size fractions of granules produced in MMG. On closer examination, greater variations in the binder contents of melt granules could be observed at shorter massing times of 10 and 14 min where binder content fell as low as 10.0 and 12.5% (*w*/*w*) for melt granules less than 180 μm in size. Greater consistencies in the binder contents of granules comparable to those in CMG were achieved only when massing time was increased to 16 and 18 min. In addition, it was evident from the larger error bars that greater inter-batch variations in the binder contents of melt granules were observed for MMG as compared with CMG. This implied that the batch to batch reproducibility in binder distribution was relatively poorer in MMG.

These findings were believed to be a direct consequence of heat being dissipated nonuniformly within the powder masses under the influence of microwave radiation. As was previously reported (4), greater inter-batch variations in product temperatures were observed in MMG as compared with CMG, arising from the vastly different dielectric losses and thus microwave-induced heating capabilities of the powder mixture and surrounding air. This provided supporting evidence that the poorer batch to batch reproducibility in binder distribution was attributed to heating irregularities of the air-powder mixture when microwaves were employed. Coupled with their low heat acquisition rates, the heating nonuniformities of the air-powder mixtures resulted in the molten binder remaining viscous, thus spreading less readily and uniformly. As a result, its effective distribution became reliant on the effects of mixing and shearing which served not only to further reduce the size of the molten binder droplets to aid distribution but also to provide a supplementary source of frictional heat to assist binder activation. Indeed, massing time was found to be a critical factor influencing the distribution of binder among the different size fractions of granules in MMG. This was supported by a negative correlation (Pearson correlation coefficient, $R=-0.965$, $p<0.05$) between massing time and the standard deviation of the binder contents of the different size fractions of granules. The standard deviation provides information on the extent to which the binder contents of the different size fractions of melt granules produced at identical massing times differed from each other. This indicated that as massing duration increased in MMG, the molten binder material became more uniformly distributed within the powder masses leading to an improvement in content homogeneity. At 18 min, homogeneous distribution of binder similar to that attained in CMG was achieved for the microwave process. No corresponding correlations were detected in CMG. It could be inferred from these results that the different heating strategies employed in MMG and CMG influenced the distribution of molten binder during granulation. Its implications on the physicochemical properties and compaction behavior of resultant melt granules would be discussed in the subsequent sections.

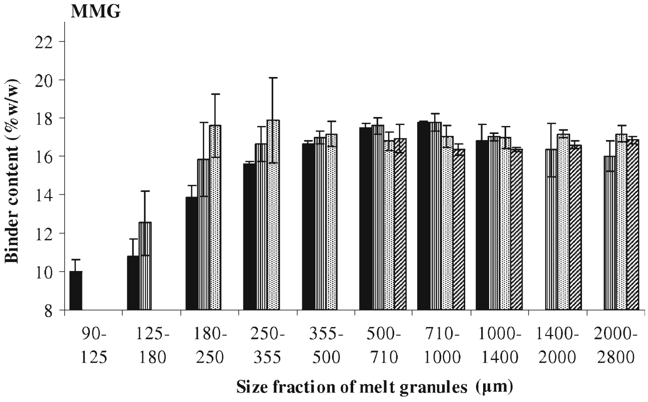

Fig. 2. Binder contents of the different size fractions of melt granules produced in MMG at massing times of 10 (■), 14 (▥), 16 (▨), and 18 min (░)

Moisture Contents of Melt Granules

From Karl Fischer analyses, the moisture contents of all melt granules ranged from 2.23 to 2.50% (*w*/*w*). This was marginally lower than the moisture content of the starting powder mixture which was found to be 2.61% (*w*/*w*) based on an identical method of analysis. Given the conditions of reduced pressure (80 mbar) and elevated temperatures (55–60°C) under which melt granulation was performed in the high shear mixer, evaporative moisture losses were expected. The relationships between the sizes and moisture contents of melt granules produced in MMG and CMG are shown in Fig. 3.

For both MMG and CMG, moisture content increased with granule size, and this was likely to be attributed to the gradual reduction in surface area available for moisture loss as agglomeration proceeded. The size and moisture contents of melt granules in MMG were strongly correlated (Pearson correlation coefficient, $R=0.996$, $p<0.01$). For CMG however, the trend was nonlinear. Therefore, the decrease in moisture loss with increased granule size appeared less marked in CMG, indicating that moisture was removed less readily from melt granules prepared in the latter process as compared with corresponding granules of similar size in MMG.

In view of the greater heating efficiencies and higher product temperatures attained in CMG (4), these findings were surprising as the thermal environment afforded in CMG was more favorable for evaporative moisture loss from the melt granules. The different agglomeration propensities in MMG and CMG could account for the observed moisture variation. In CMG, agglomerate growth proceeded more spontaneously due

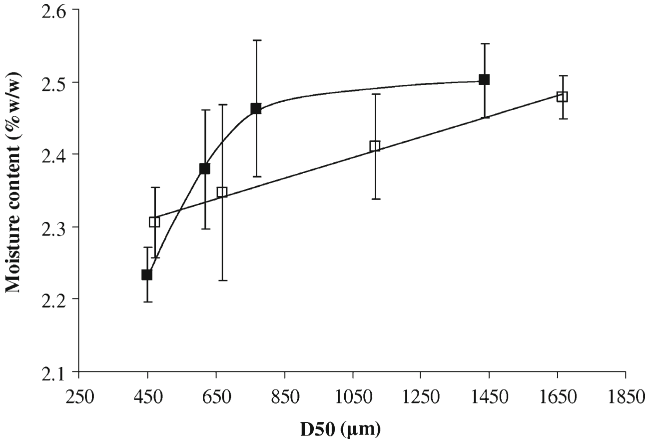

Fig. 3. Relationship between the size and moisture content of melt granules in MMG (*empty squares*) and CMG (*filled squares*)

to the enhanced heating capabilities of the powder masses under the influence of the heated mixer bowl (4). The higher rate of growth and rapid transformation of smaller to larger granules resulted in greater moisture entrapment which contributed to the higher residual moisture contents in the resultant granules. To compensate for the heating inefficiencies of the powder masses in MMG, longer massing durations of 10–18 min were required for growth induction and production of granules that were of comparable size to those in CMG (4). Granule formation proceeded at a more gradual pace and the transformation of smaller to larger granules occurred with less haste in MMG. More time was available for moisture losses during the earlier stages of agglomeration when the granules were small and possessed a larger surface area. This, coupled with the constant input of mechanical energy from the high-speed impeller for prolonged durations, provided greater leeway and opportunities for evaporative moisture losses. Excitation and subsequent evaporation of water molecules arising from the selectivity of microwaves for water may also have contributed to the lower residual moisture contents of melt granules produced in MMG.

Influences of the Physicochemical Properties of Melt Granules on Their Compaction Behavior

The flow properties (bulk and tapped densities, Hausner ratios as well as compressibility indices) and porosities of melt granules produced in MMG and CMG are presented in Table II. Their compaction behavior, as reflected by the porosities of compacts formed under a compaction pressure of 102 MPa, is similarly shown. Generally, all melt granules produced possessed excellent flow and their porosities ranged from 49% to 54%. The mechanical strengths and porosities of resultant compacts ranged from 110 to 142 N and 4.8% to 6.1%, respectively.

Multivariate data analysis was employed to assess the influences of the various physicochemical properties of melt granules on their compaction behavior. In addition to their flow properties and porosities as shown in Table II, the physicochemical properties of melt granules also encompassed their size and size distribution (mass median diameters, spans and proportion of fines as listed in Table I), binder as well as moisture contents as discussed earlier. As an un-sieved sample of melt granules was compacted each time, the binder content of melt granules (un-sieved) was derived from the summation of the weighted contributions of the binder contents of the different size fractions of granules as shown in Figs. 1 and 2. The inter-variable relationships among the physicochemical properties of melt granules, mechanical strengths and porosities of the corresponding compacts formed under a compaction pressure of 102 MPa are depicted in the loadings plots in Figs. 4 (CMG) and 5 (MMG).

The loadings plots were interpreted based on the spatial distribution of the variables of interest with respect to each other and the principal component axes. Variables situated close together in a loadings plot co-vary positively while those situated on opposing ends are negatively correlated to each other. Variables which overlap or are indistinguishable from each other are strongly and positively correlated. Variables orthogonal (perpendicular) to each other, on the other hand, are independent (10). "X-expl: 83%, 10%" (Fig. 4) meant that the first two principal components, PC1 and PC2, accounted for 93% of the total variance in the data obtained from CMG whereas "X-expl: 79%, 16%" (Fig. 5) implied that both these principal components accounted for 95% of the total variance in the data set obtained from MMG. These values meant that the majority of the variations and trends underlying the processes of MMG and CMG could be explained using the first two principal components. This eliminated the need to analyze higher order components (10).

At the outset, it was clear from both loadings plots that the size distribution of melt granules produced in the two processes exerted minimal influences on their compaction

Table II. Flow Properties and Porosities of Melt Granules Produced in MMG and CMG as well as the Porosities of the Corresponding Compacts Prepared Under a Compaction Pressure of 102 MPa

Process	Massing time (min)	BD[a] (g/ml)	TD[a] (g/ml)	HR[a]	CI[a] (%)	ϵgr [a] (%)	ϵcom[a] (%)
MMG	10	0.800 (0.073)	0.869 (0.032)	1.09 (0.06)	8.08 (5.04)	53.13 (1.72)	6.10 (0.44)
	14	0.867 (0.048)	0.912 (0.039)	1.05 (0.01)	5.00 (1.29)	50.81 (2.02)	4.84 (0.26)
	16	0.918 (0.015)	0.943 (0.018)	1.03 (0.01)	2.67 (0.76)	48.77 (1.23)	4.38 (0.33)
	18	0.865 (0.047)	0.909 (0.026)	1.05 (0.03)	4.92 (2.62)	50.67 (1.30)	4.64 (0.30)
CMG	6	0.807 (0.008)	0.858 (0.005)	1.06 (0.02)	6.00 (1.32)	53.82 (0.36)	5.72 (0.22)
	8	0.826 (0.028)	0.869 (0.012)	1.05 (0.02)	5.00 (2.00)	53.05 (0.69)	5.50 (0.19)
	10	0.852 (0.036)	0.893 (0.021)	1.05 (0.02)	4.67 (2.02)	51.85 (1.35)	5.38 (0.20)
	12	0.901 (0.026)	0.935 (0.037)	1.04 (0.01)	3.67 (1.04)	49.55 (1.98)	5.33 (0.18)

BD bulk density of granules, *TD* tapped density of granules, *HR* Hausner ratio of granules, *CI* compressibility index of granules, *ϵgr* porosity of granules, *ϵcom* porosity of compact prepared under a compaction pressure of 102 Mpa

[a] Standard deviations are indicated in the parentheses

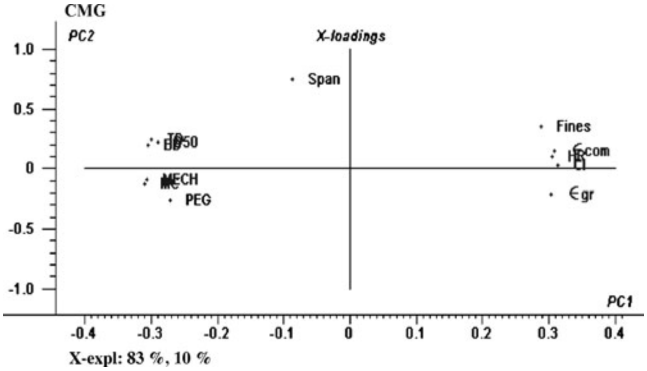

Fig. 4. Loading plot depicting the inter-variable relationships among the various physicochemical properties of melt granules produced in CMG as well as the porosities and mechanical strengths of corresponding compacts. Abbreviated parameters are: *D_{50}* mass median diameter of granules (μm), *BD* bulk density of granules (g/ml), *TD* tapped density of granules (g/ml), *HR* Hausner ratio of granules, *CI* compressibility index of granules (%), *Єgr* porosity of granules (%), *PEG* binder content of granules (% *w*/*w*), *MC* moisture content of granules (% w/w), *Єcom* porosity of compact (%) prepared under a compaction pressure of 102 MPa, *MECH* mechanical strength of compact (*N*) prepared under a compaction pressure of 102 MPa. The span and proportion of fines (%) are not abbreviated

behavior. This could be gauged from the orthogonal relationship of "Span" with respect to the porosities (Єcom) and mechanical strengths (MECH) of compacts observed in both Figs. 4 and 5. Fundamentally, particle densification constitutes an important preliminary step towards agglomerate growth in high shear granulation. This was reflected in the loadings plot for CMG (Fig. 4) where the opposing locations of "D_{50}" with respect to both "Fines" and "Єgr" indicated that agglomerate growth (increased D_{50}) was accompanied by reductions in the proportion of fine particles and granule porosity (Pearson correlation between D_{50} and Єgr, $R=-0.988$, $p<0.05$). Granule porosity in turn, correlated significantly with their compressibility indices (Pearson correlation between Єgr and CI, $R=0.963$, $p<0.05$) and this indicated that larger and denser granules possessed improved flow and packing properties. When a denser granular bed was achieved in the die cavity, the intergranular void spaces were minimized and this increased the specific surface area available for intergranular attraction and bonding during compaction. Denser compacts with reduced porosities were thus formed. As the porosities of compacts decreased, their mechanical strengths increased. This could be inferred from the opposing locations of "MECH" and "Єcom" in the loadings plot (Pearson correlation between Єcom and MECH, $R=-0.998$, $p<0.01$).

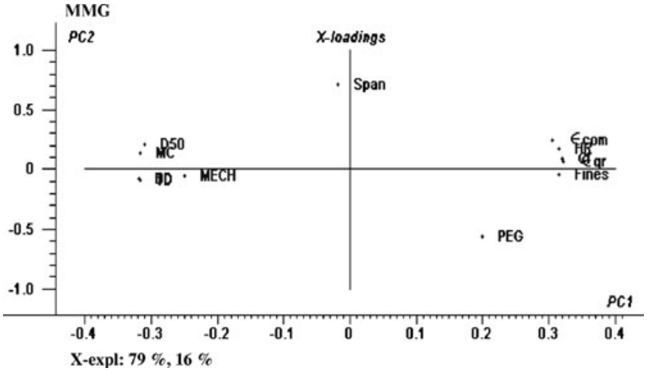

Fig. 5. Loading plot depicting the inter-variable relationships among the various physicochemical properties of melt granules produced in MMG as well as the porosities and mechanical strengths of corresponding compacts. Abbreviated parameters are: *D_{50}* mass median diameter of granules (μm), *BD* bulk density of granules (g/ml), *TD* tapped density of granules (g/ml), *HR* Hausner ratio of granules, *CI* compressibility index of granules (%), *Єgr* porosity of granules (%), *PEG* binder content of granules (% *w*/*w*), *MC* moisture content of granules (% *w*/*w*), *Єcom* porosity of compact (%) prepared under a compaction pressure of 102 MPa, *MECH* mechanical strength of compact (*N*) prepared under a compaction pressure of 102 MPa. The span and proportion of fines (%) are not abbreviated

The binder and moisture contents of melt granules produced in CMG also figured prominently in their compaction behavior. From the physical locations of "PEG" and "MC" with respect to "Єcom" and "MECH," it appeared that melt granules containing higher binder and moisture contents formed compacts of lower porosities and increased mechanical strengths (Pearson correlation between MECH and PEG, $R=0.953$, $p<0.05$; MECH and MC, $R=0.998$, $p<0.01$). Such observations were to be expected. Solid polyethylene glycols, being plastic and deformable in nature (11,12), have been widely exploited for modulating the tabletting behavior of aggregates (13) as well as providing cushioning protection to drug-coated pellets during compaction (14–16). This was achieved through the ability of the material to deform, absorb and dissipate the applied stresses effectively during compaction, thereby enhancing the compressibility of the aggregates and pellets. In addition, it has been reported that the compressibility of granules manufactured in a high shear mixer was more sensitive to their residual moisture contents after drying than to changes in processing conditions such as wet massing time and impeller speed (17). In the light of these findings, it was to be expected that both the binder and moisture contents of melt granules played significant roles in their compressibility. Melt granules containing higher binder and moisture contents were likely to be more deformable and amenable to compression. At any particular compaction pressure, these melt granules deformed more readily. This facilitated the development of larger surface areas for intergranular contact and bond formation which were responsible for the mechanical integrity of the formed compact. Thus, by way of their enhanced compressibility and deformability, melt granules containing higher binder and moisture contents formed less porous compacts of increased mechanical resilience.

Similar relationships were observed for MMG (Fig. 5). Granule growth brought about a reduction in the proportion of fines and granule porosity. Denser granules possessed better flow and improved packing properties which in turn yielded compacts with reduced porosities. Accordingly, compacts of lower porosities possessed higher mechanical strengths and *vice versa*. With regards to the influence of the moisture contents of granules, a trend similar to that in CMG was observed where melt granules containing higher moisture contents formed mechanically stronger compacts with decreased porosities. However, a slight difference was observed in MMG pertaining to the contribution of the binder contents of melt granules. It appeared from the distant location of "PEG" with respect to "Єcom" and "MECH" that the binder contents of granules in MMG exerted minimal bearing on their compaction behavior.

This anomaly was believed to be attributed to the nonuniformity in binder distribution during MMG. By pooling the data sets obtained from MMG and CMG, Fig. 6 shows the relationship between the binder contents of all batches of melt granules produced and the mechanical strengths of the resultant compacts. Apart from two distinct outliers (marked with an asterisk), a reasonable correlation (Pearson correlation coefficient, $R=0.870$, $p<0.05$) was detected between the two variables for the remaining granule batches where an increase in the binder contents of melt granules led to a corresponding increase in the mechanical strengths of the resultant compacts. The ambiguity pertaining to the effect of binder content on the compaction behavior of melt granules in MMG may be addressed by the outliers which incidentally, represented the binder contents and compaction behavior of melt granules produced at massing times of 10 (MMG10) and 14 min (MMG14). Based on the mechanical strengths of the compacts, the melt granules possessed unexpectedly higher binder contents. The melt granules derived from the same process but at longer massing times of 16 and 18 min conformed to the general trend exhibited by the remaining granule batches and compacts derived from CMG.

Based on these results, it may be inferred that in MMG, the effect of the binder contents of melt granules on their compaction behavior was masked by the deviation from the expected trend, of the melt granules produced at specific massing times of 10 and 14 min. A likely explanation for this nonconformity stemmed from issues related to content homogeneity. As discussed earlier, the binder was distributed less uniformly among the different size fractions of granules in MMG as compared with CMG. Specifically, melt granules produced at shorter massing times of 10 and 14 min in MMG exhibited greater levels of binder heterogeneity. Under these circumstances, each compact prepared from granules produced at these particular massing times may not have contained the amount of binder material that was calculated based on the different size fractions of melt granules. This was because a much smaller quantity of melt granules (~0.5 g) was used for each compaction cycle as compared to that for size analysis (~100 g) and thus the melt granules sampled for compaction may not contain the different size fractions of melt granules in their representative proportions. Since disparities existed among the binder contents of the different size fractions of melt granules, discrepancies were likely to arise between the calculated amount of binder material based on the weighted contributions of the binder contents of the different size fractions of melt granules obtained from size analysis and the actual content of binder in the formed compacts. Thus, the MMG experiments performed at specific massing times of 10 and 14 min masked the effect of the binder contents of melt granules on their compaction behavior which would have otherwise surfaced in the loadings plot in Fig. 5.

Compressibility of Melt Granules

The data presented in Fig. 6 provided the first signs of evidence that the disparities in compaction behavior of melt granules produced in MMG and CMG were attributed in part, to the differences in their binder contents. To gain further insight and to quantify these effects, the compressibility of selected batches of melt granules produced from the two processes were studied by subjecting the melt granules to compaction pressures ranging from 13 to 304 MPa. As aforesaid, melt granules prepared at shorter massing times in MMG were plagued by higher levels of binder heterogeneity. Hence, those produced at the longest massing time, *i.e.*, 18 min (MMG18) were chosen for compressibility studies to circumvent this problem and ensure greater validity of the results. Moreover, melt granules from MMG18 exhibited the closest conformity to the general trend in Fig. 6. For CMG, melt granules produced at massing times of 6 and 10 min were selected (CMG6 and CMG10, respectively). The rationale for these choices was that the binder contents of melt granules manufactured under these three specific conditions (MMG18, CMG6, and CMG10) spanned a wider range and encompassed the higher, lower and intermediate ranges of binder contents among all the batches of melt granules eligible for assessment.

The Heckel plots of these melt granules are presented in Fig. 7. From the steep linear portions of the profiles at the initial stages of compaction (13–63 MPa), it was evident that the melt granules underwent extensive volume reduction early in the process. Beyond 100 MPa, volume reduction of the granule bed became almost negligible. It is well known that both lactose and DCP are brittle materials which undergo fragmentation during compaction (18–21). Interest-

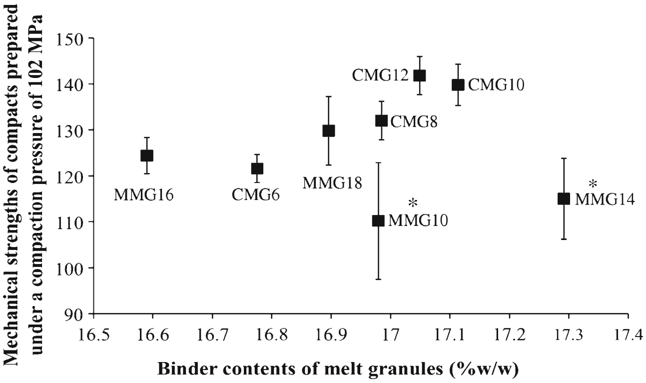

Fig. 6. Effect of the binder contents of melt granules produced at different massing times in CMG and MMG on the mechanical strengths of corresponding compacts prepared under a compaction pressure of 102 MPa. *Asterisk* refers to the outliers

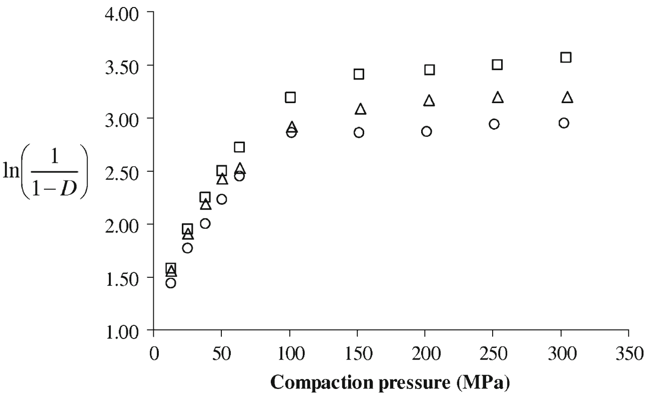

Fig. 7. Heckel plots of selected batches of melt granules produced in CMG at 6 (*empty circles*) and 10 min (*empty triangles*) as well as MMG at 18 min (*empty squares*)

ingly however, the compaction profiles of the melt granules conformed to the type C variant of the Heckel plot which indicated that they consolidated by plastic flow (22).

Clearly, the presence of a soft, waxy and plastically deforming material such as polyethylene glycol 3350 in the lactose and DCP-based granules caused significant modifications to their volume reduction behavior and changed it from one that was primarily fragmenting to another dominated by plastic deformation. This phenomenon has been reported in studies that involved the compaction of powder mixtures comprising both fragmenting and plastically deforming materials. In these systems, it was found that plastic flow exerted more pronounced effects on volume reduction than fragmentation (19). It has also been reported that when polyethylene glycol was incorporated as a binding agent in granules, both in solution (polyethylene glycol 6000) and molten form (polyethylene glycol 6000 and 20000) in wet and melt granulation, respectively, the deformation tendencies of resultant granules were enhanced significantly (13,23). These observations were most likely to be due to the low yield pressures of polyethylene glycols (21) which render them highly susceptible to deformation even at low compaction pressures. Compaction studies of pure polyethylene glycol 10000 (8,24) revealed that the majority of volume reduction occurred at low pressures ($\leq$82 MPa) where a predominantly linear profile was observed during the initial stages of compaction following which changes in powder volume, if any, were minimal or negligible as compaction pressure increased. This information is consistent with the pronounced volume reduction of melt granules observed at pressures below 100 MPa.

Further evidence that supported the predominance of plastic deformation rather than fragmentation as the main mechanism of volume reduction of the melt granules pertained to the effects of the porosities of granules on their compaction behavior. In compaction studies of agglomerates comprising materials which are brittle and fragmenting in nature, agglomerates of higher porosities typically exhibited greater fragmentation propensities and formed compacts which were mechanically stronger and less porous. These were attributed to the increased surface areas available for inter-particulate bonding as a result of particle fragmentation (25–28). Interestingly however, a trend reversal was observed in the current study where granules of lower porosities formed compacts of increased mechanical strengths instead. As depicted earlier in Figs. 4 and 5, this was mediated through the improved packing properties of the denser granules in the die cavity. These findings provided a clear indication that up to a compaction pressure of 102 MPa, granule fragmentation was not the predominant mechanism responsible for the volume reduction and compaction behavior of melt granules. The critical underlying factors were the amount and availability of binding material in the melt granules which affected the extent to which they could deform and fill up existing intergranular void spaces to facilitate bonding interactions among the granules in the die cavity.

Taking a step further, the yield pressures of melt granules were computed. Regression analyses were performed over the pressure ranges of 25–63 MPa for melt granules produced at 6 and 18 min in CMG (CMG6) and MMG (MMG18), respectively. A lower pressure range of 13–50 MPa was selected for melt granules produced at 10 min in CMG (CMG10). These ranges were employed as the experimental data points possessed the highest goodness-of-fit (R^2) values. The linear equations together with the corresponding yield pressures of granules are summarized in Table III. It had been reported that materials with yield pressures of less than 80 MPa deformed mainly by plastic flow and as the value increased beyond this limit, there was an increased likelihood of material fragmentation (29). The yield pressures of the melt granules ranged from 43.9 to 55.6 MPa which were significantly lower than 80 MPa and those of pure α-lactose monohydrate (~200 MPa) or DCP (~550 MPa) (30,31). This further attested to their plastic nature.

As mentioned earlier, the residual moisture present in the melt granules also enhanced their tendencies to deform plastically. As both the binder and moisture contents of melt granules were expressed in an identical manner (% *w*/*w*), they were summed up to provide a measure of the total fraction by weight of melt granules that were composed of these two components. A negative correlation (Pearson correlation coefficient, $R=-0.999$, $p<0.05$) was obtained between the combined binder and moisture contents of the granules and their yield pressures. Melt granules possessing the highest combined binder and moisture contents, *i.e.*, CMG10, exhibited the lowest yield pressure and *vice versa*. Clearly, the influences of the binder and moisture contents of melt granules on their compressibility were mediated through their effects on the yield pressures of granules. Being most deformable upon compaction, melt granules produced in CMG10 formed compacts of highest mechanical strength (139.8 N), followed by those produced from MMG18 (129.8 N) and CMG6 (121.6 N) in decreasing order.

CONCLUSIONS

The different heating strategies employed in MMG and CMG resulted in dissimilarities in the physicochemical properties and compaction behavior of the resultant melt granules. The lower heat acquisition rates and heating nonuniformities of the powders in MMG hampered agglomerate growth and binder distribution. Thus, longer massing durations were necessary for growth induction, with greater inter-batch variations in binder contents of melt granules and decreased uniformity in binder distribution among the different size fractions of granules. In CMG, the powder masses heated more efficiently and uniformly resulting in shorter processing times and improved content homogeneity. Evaporative moisture losses from the melt granules occurred more readily in MMG due to the longer massing durations as well as the slower rate of agglomeration. With respect to the compaction behavior of granules, it was found that larger and

Table III. Equations Governing the Linear Portions of the Heckel Plots and Corresponding Yield Pressures of Selected Batches of Melt Granules

Type of melt granules	Equation	R^2	Yield pressure (MPa)
CMG6	$y=0.018x+1.318$	1.000	55.56
CMG10	$y=0.0228x+1.300$	0.993	43.86
MMG18	$y=0.0201x+1.464$	0.995	49.75

denser granules flowed better and formed compacts of lower porosities and increased mechanical strengths. The binder and moisture contents of melt granules affected their volume reduction behavior and were responsible for the disparities in compaction behavior of melt granules produced from MMG and CMG. Melt granules containing higher binder and moisture contents possessed lower yield pressures and deformed more readily upon compaction. This led to greater extents of inter-particulate bonding and formation of mechanically stronger compacts.

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