Process Control in a High Shear Mixer-Granulator Using Wet Mass Consistency: The Effect of Formulation Variables

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Abstract □ This work investigates the relationships between the wet mass consistency/viscosity of samples prepared in a mixer-granulator and physical properties of the dry granules produced from the wet mass; namely, size distribution, bulk density (Hausner ratio), friability, and flow avalanching behavior. The correlation between the consistency of the wet mass and the downstream dry granule properties confirms that consistency is the key parameter to control in wet granulation by mechanical agitation. Variations in the formulation affect the dimensionless power relationship of the mixer-granulator considered; that is, the equivalence between wet mass consistency and mixer net power consumption, which is actually the parameter used to monitor the wet granulation process. The same variations in formulation also affect the relationships between wet mass consistency and dry granule properties.

Introduction

Over recent years, a strategy based on the use of dimensionless numbers has been designed to allow a better control and scale-up of wet granulation processes in pharmaceutical mixer-granulators.[1−4] The granulation end point is classically detected by monitoring the power consumption of the mixer-granulator. In this new approach, a dimensionless power relationship is determined that summarizes the overall effect of various process parameters linked to the wet mass and to the mixer-granulator itself. Hence, knowing the wet mass characteristics wanted and the conditions in which the mixer is to be operated, the dimensionless power relationship is employed to give the corresponding target power consumption value that will signal the end point of the granulation.

However, several assumptions are made in this approach. In particular, the wet mass has to be considered as a continuous phase, which is described solely by the composition of its dry formulation, its wet bulk density, and viscosity. The viscosity of the wet mass is assessed using a mixer torque rheometer, an instrument that has been specifically developed to quantify the rheological consistency of the pharmaceutical wet masses.[4,5] It has been demonstrated that wet mass consistency was linearly proportional to wet mass viscosity,[5] while offering the advantage of being easier to measure. Intrinsically, it is also assumed in the methodology that if the wet mass quality can be reproduced, through the control of the wet mass consistency, then the quality of the dry granules produced downstream from the wet mass will also be controlled. This assumption presupposes that there exists a link between the wet mass consistency and the dry granule characteristics.

The objective of this work was to verify this assumption by proving the existence of a relationship between the wet mass consistency and several dry granule properties judged important with regards to tableting. The effect of formulation on the dimensionless power relationship of a given mixer-granulator will also be investigated.

Experimental Section

The wet mass samples were produced in a pharmaceutical, high-shear mixer-granulator (Aeromatic Fielder PMA 100 L, Eastleigh, Hampshire, UK) using five different hydrophilic formulations, coded as 'R', 'L', 'P', 'C', and 'D' and defined in Table 1. Lactose 450 mesh (DMV International, Veghel, The Netherlands), starch (National Starch and Chemical GmbH, Neustadt, Germany), pregelatinized starch (PGS, National Starch and Chemical GmbH, Neustadt, Germany), and dibasic calcium phosphate dihydrate (DCPD, Calipharm, UK) were generously supplied by Zeneca Pharmaceuticals. Lactose 200 mesh was a gift from DMV International, Veghel, The Netherlands. Poly(vinylpyrrolidone) (PVP K25) was supplied by BASF, Ludwigshafen, Germany.

Wet massing runs were carried out at different impeller speeds, whereas water was sprayed at a constant rate. The spray nozzle and the water flow rate were chosen to ensure a quick distribution of the water among the mix. Samples were withdrawn at regular intervals to give a range of increasing consistency values and were immediately analyzed for their bulk density and consistency.

The consistency was determined using a mixer torque rheometer (Caleva MTR, Sturminster-Newton, Dorset, UK) as previously described by Rowe and Parker,[4] run at a shaft speed of 50 rpm. A baseline was recorded for 20 s, then 35 g of wet sample was introduced and mixed for 30 s, and then data were recorded for 30 s. The wet mass consistency of the sample was calculated as the mean torque value recorded with the sample in the mixer less the mean torque value of the baseline recording. All reported values were the average of two determinations.

To obtain dry granules for further analysis, the wet mass samples were subsequently processed, by first passing through a 1000 μm screen, then tray-drying in an oven at 40 °C for 24 h, and finally screening once again through a 850 μm sieve. The undersized fractions were analyzed for size distribution (by sieve analysis); apparent bulk density (aerated and tapped to derive their Hausner ratio); flow (using an Aero-Flow, Amherst Process Instruments, Hadley, MA), based on an avalanching principle;[6] and friability index (using a modified test procedure in a Roche tablet friability test apparatus). The densities were determined in a tapping apparatus similar to that described in the European Pharmacopoeia (second edition, V.5.5.4.). The Aero-Flow measures the time intervals between avalanches generated within a granule sample placed in the slow rotating drum of the apparatus. The assay was made with the 1−600-μm fractions of the samples. The quantity used varied according to the density of the formulation, with 25 g for the lactose-based and 40 g for the DCPD-based formulations. Compilation of the frequency and irregularity of

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Table 1—Composition of the Different Powder Mixes Granulated[a]

formulation	lactose/DCPD	maize starch, %	PGS/PVP	composition
R	450 mesh 80%	18	PGS 2%	reference formulation
L	200 mesh 80%	18	PGS 2%	same source of lactose but different grade, with larger particles
P	450 mesh 80%	18	PVP 2%	same as reference formulation except binder (water soluble grade of PVP)
C	DCPD 80%	18	PGS 2%	filler replaced by an inorganic, water-insoluble but still hydrophilic filler
D	450 mesh DCPD 40% + 40% 450 mesh lactose	18	PGS 2%	intermediate composition between 'R' and 'C' formulations

[a] % indicated are on a weight basis.

these time intervals was then used to describe the flow behavior of the sample. In the friability test, 10 g of sample was used regardless of formulation, and the Roche tablet friabilator was run 5 min at 90 rpm with a sample and five small glass balls. The glass balls had a mean diameter of 16 mm and a density of 2.34 g/cm^3. They were preferred to lighter materials (plastic and wooden balls) to maximize the differences in results obtained from various granule samples. The friability index was taken as $100 - x$%, where x is the percentage of the original sample fraction 250–600 μm retained by a 250 μm sieve after testing. Similar methods are encountered in the literature with various drum speeds, sample sizes, and sieve fractions, and presence or absence of inert balls.[7–9] Mechanically stronger granules produce a lower friability index.

Results and Discussion

The dimensionless power relationship of the mixer-granulator gives the relationship between the power consumption of the mixer and the wet mass consistency. The following expression will be used:[2]

$$\log_{10} \mathrm{Np} = a + b^{*}\log_{10} (\Psi\mathrm{Re}^{*}\mathrm{Fr}^{*}\text{fill ratio}) \qquad (1)$$

where Np is the Power number

$$\mathrm{Np} = \frac{\Delta P}{\rho N^3 R^5} \qquad (2)$$

ΨRe is the pseudo Reynolds number

$$\Psi\mathrm{Re} = \frac{\rho N R^2}{\mu} \qquad (3)$$

Fr is the Froude number

$$\mathrm{Fr} = \frac{R N^2}{g} \qquad (4)$$

and fill ratio indicates the fraction of bowl working capacity occupied by the wet mass, and can be represented, for example, by[2]

$$\frac{\rho R_\mathrm{B}^3}{m} \qquad (5)$$

The dimensionless numbers 2 to 5 are defined with the following notations:

ΔP = the net power consumption of the mixer-granulator (W)

(total power consumption less power required to stir the dry mix)

m = the amount of wet mass (kg)

ρ = the wet mass bulk density (kg·m^{-3})

μ = the wet mass consistency (Nm)

N = the impeller rotational speed (s^{-1})

R = the impeller radius (m)

R_B = the bowl radius (m)

g = the gravitational constant (9.81 ms^{-2})

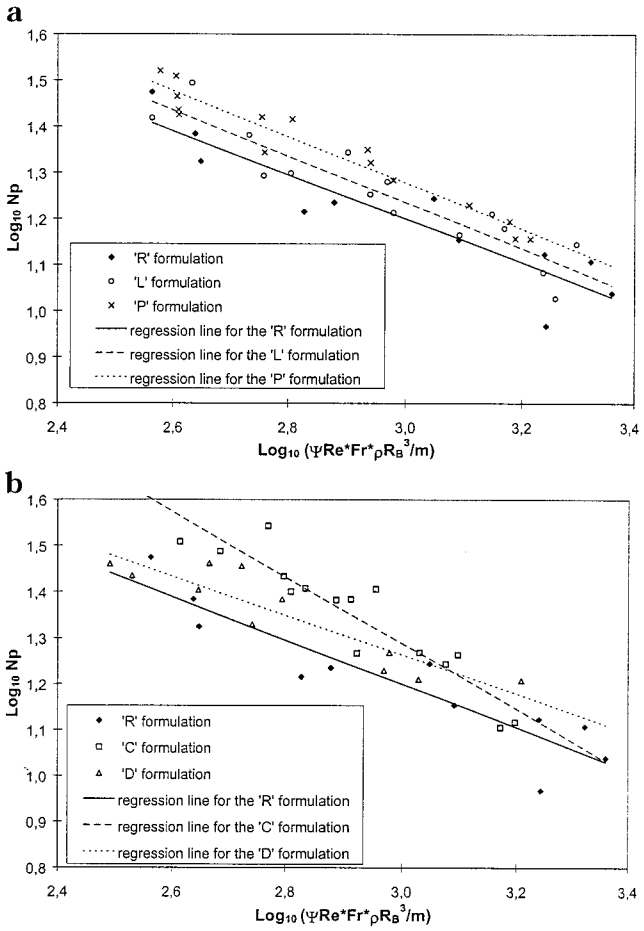


Figure 1—Scale-up relationships obtained for the five formulations tested in the Fielder PMA 100 L mixer-granulator.

Data from the experimental granulation runs were used to determine the dimensionless power relationship of the Fielder PMA 100 L mixer-granulator and to investigate the effect of formulation on this relationship. The results are graphically presented in Figures 1a and b. The statistical analysis on the regression lines was compiled using a statistical software package (SPSS 6 for Windows, SPSS UK Ltd, Chertsey, Surrey, UK) and the results are summarized in Table 2.

No statistical difference can be seen between the regression lines of the three lactose formulations. This result indicates that the dimensionless power relationship is little affected by the change of binder, from PGS to PVP, or by the change of filler particle size from lactose 450 mesh to lactose 200 mesh.

The slope and intercept of the regression line for the 'C' formulation, DCPD based, are distinct from these of the corresponding lactose 'R' formulation. Note, however, that as the confidence limits are determined at ± 1 standard deviation, the observations made are only at 68% confidence. At 95% confidence (i.e., $p = 0.05$), with the confi-

Table 2—Scale-up Regression Line Results[a]

formulation	a	σ_a	interval of confidence for a[b]	b	σ_b	interval of confidence for b	r^2[c]	n[d]
'R'	–0.473	0.067	[–0.540; –0.406]	2.620	0.202	[2.418; 2.822]	0.847	11
'L'	–0.500	0.057	[–0.557; –0.443]	2.734	0.170	[2.564; 2.904]	0.855	15
'P'	–0.499	0.037	[–0.536; –0.462]	2.775	0.105	[2.670; 2.880]	0.935	15
'C'	–0.717	0.079	[–0.796; –0.638]	3.439	0.230	[3.209; 3.669]	0.864	15
'D'	–0.426	0.064	[–0.490; –0.362]	2.542	0.178	[2.364; 2.720]	0.833	11

[a] $\text{Log}_{10}\text{Np} = a\ \log_{10}[\Psi\text{Re}\cdot\text{Fr}\cdot\rho R_B^3/m] + b$. [b] The confidence limits were calculated at ± one standard deviation (σ). [c] Regression coefficient. [d] Number of data points.

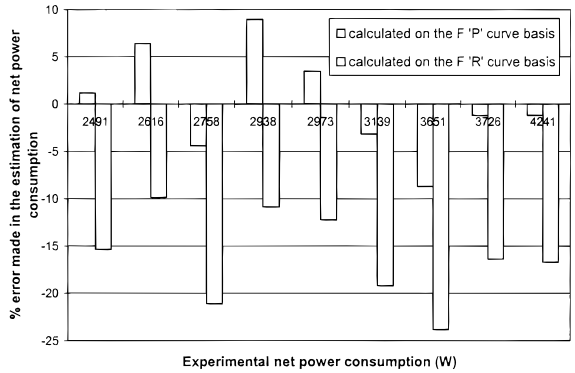


Figure 2—Percentage of error made on the net power consumptions of the 'P' formulation samples when the dimensionless power relationship of this formulation and of the 'R' formulation are used.

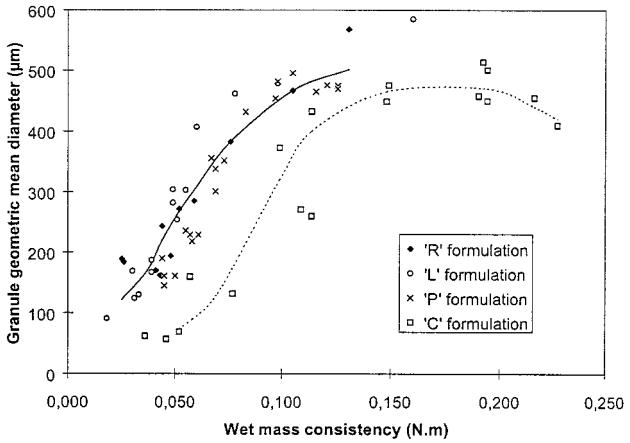


Figure 3—Relationship between the wet mass consistency and the dry granule geometric mean diameter by weight.

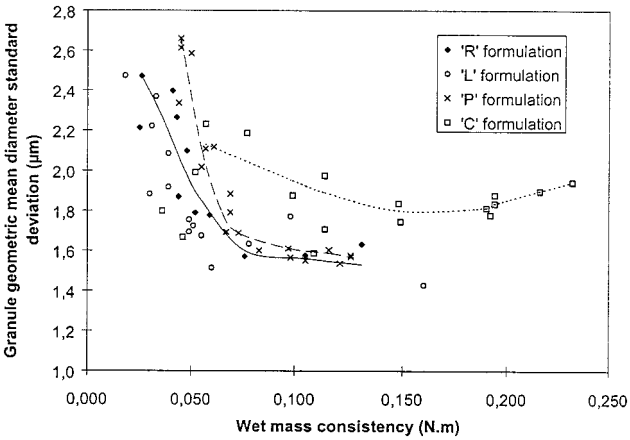


Figure 4—Relationship between the wet mass consistency and the dry granule size distribution standard deviation.

dence limits at ±1.96 standard deviation, the comparisons between slope and intercepts of the 'C' and 'R' regression lines are inconclusive.

When half the DCPD in the 'C' formulation is replaced by lactose 450 mesh ('D' formulation), the effect of this variation of filler on the slope and intercept of the regression line is again not significant. Interestingly the 'D' formulation does not behave intermediate to the 'C' and 'R' formulations but, on the contrary, would tend to present a curve similar to these of the lactose formulations.

To verify the quality of the model, or in other words the accuracy of the target net power consumption deduced from the dimensionless power relationship of the bowl, the case of the 'P' formulation was further studied. Figure 2 represents the percentage of error made in the estimation of ΔP with regards to the real value of ΔP measured experimentally, when the dimensionless power relationships specific to this formulation and the 'R' formulation are respectively used. Figure 2 shows that the dimensionless power relationship specific to the 'P' formulation permits a good prediction of the net power consumption, usually within 5% of error. On the other hand if the relationship established for the 'R' formulation is used, then the predicted power consumption value is systematically underestimated by around 10−20%. For scale-up purposes (i.e., when considering other geometrically similar bowls in the same series of mixer-granulators), it is therefore important to determine the dimensionless power relationship specific to the formulation considered to determine workable power consumption predictions.

In the remainder of this work, the dry granules obtained from the granulation runs on the different formulations were compared to study the link between the consistency of the mass prior to drying and the quality of the downstream granules, and to investigate once again the effect of varying the formulation.

Figures 3 to 6 illustrate the relationships found between the wet mass consistency and different dry granule properties; they are, geometric mean diameter by weight and its standard deviation, Hausner ratio, and friability index. With these tests no significant differences are seen between the three lactose formulations investigated, despite the change in binder composition (PVP or PGS) or in filler particle size (volume median diameter of lactose 450 and 200 mesh were respectively found to be 26 and 44 μm by laser diffraction, Malvern Instruments, Malvern, Worcestershire, UK). Only the granule size distribution of the 'P' formulation is slightly wider than that of the other two lactose formulations, at low levels of granulation (i.e., low wet mass consistency values).

The DCPD-based formulation, 'C', shows a distinct trend for granule size distribution and friability. Higher wet mass consistency values are required to obtain dry granules of a given size compared with the lactose formulation. The 'C' formulation is also more friable than its lactose counterparts, probably due to the absence of a 'secondary binder' effect. DCPD is indeed insoluble in water, the solvent used for granulation, whereas lactose is partially soluble and contributes therefore to the strength of the final dry bridges. The 'D' formulation, made up in equal parts of lactose 450 mesh and DCPD, was only analyzed for

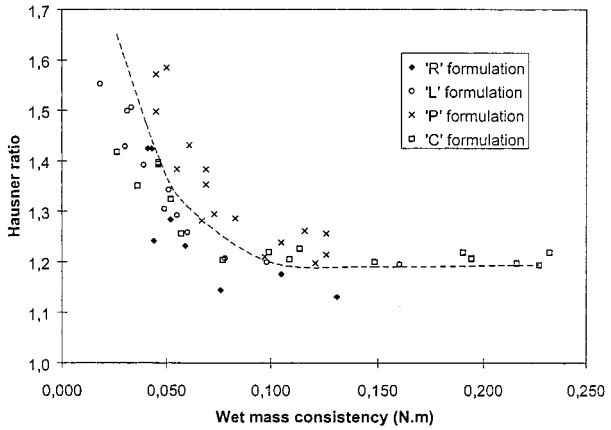


Figure 5—Relationship between the wet mass consistency and the dry granule Hausner ratio.

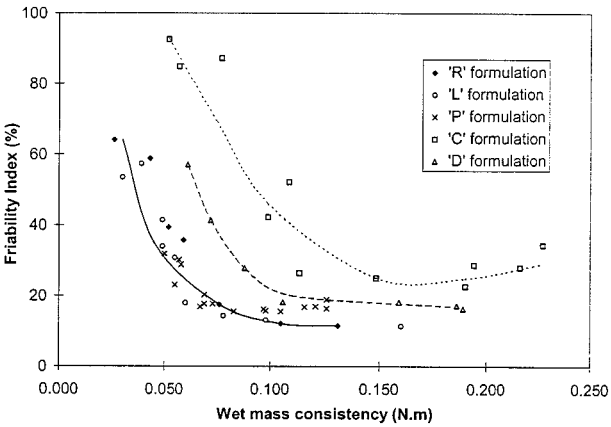
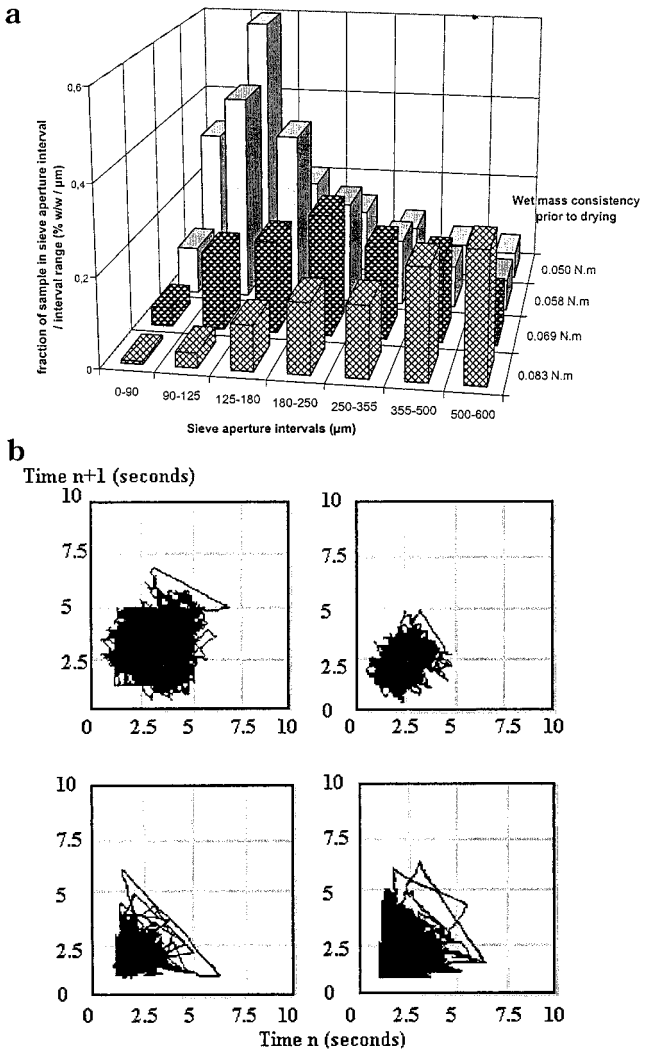


Figure 6—Relationship between wet mass consistency and the dry granule friability index.

friability. It behaved somewhat intermediate to the 'R' and 'C' formulations, except at high wet mass consistency values, where the level of moisture is such that the lactose contribution to the granule strength was almost comparable to a pure lactose formulation. The differences found between the lactose- and DCPD-based formulations are unlikely to be due to the variation in initial particle size (volume median diameter of 14 μm for DCPD), as there was already no difference in the wet mass consistency/dry granule properties relationships between the 'R' and 'L' formulations.

Overall, it is observed that the dry granule properties considered vary almost linearly with the consistency of the original wet mass, up to approximately 0.08 Nm for the lactose-based formulations, and 0.12 Nm for the 'C' formulation. Above these respective values, further addition of binder liquid (water) does not significantly affect the granule growth and densification (granule geometric mean diameter, standard deviation, and Hausner ratio all roughly level off). Additionally, the mechanical strength of the dry granules stops improving at exactly the same levels of wet mass consistency.

The flow avalanching behavior of the granules was analyzed using the Aero-Flow. As an example, the patterns obtained for different samples prepared from one granulation run with the 'P' formulation are shown in Figure 7a. These graphical representations are compiled by plotting the time between avalanches number n and $n+1$ ('time n+1') against the time between avalanches number $n-1$ and n ('time n'), for $1 < n < n_t - 1$, where n_t is the total number of avalanches recorded during the analysis. Such plots are characterized by their centroid, representing the



Wet mass consistency:

a. 0.050 N.m b. 0.058 N.m c. 0.069 N.m d. 0.083 N.m

Mean time between avalanches:

a. 3.13 s b. 2.34 s c. 1.74 s d. 1.68 s

Irregularity factor:

a. 1.05 s b. 0.60 s c. 0.43 s d. 0.51 s

Figure 7—Example of granule size distribution and corresponding flow patterns observed on four granule samples of increasing wet mass consistency (taken for the same granulation run at 180 rpm with the 'P' formulation).

mean time between avalanches, and the scatter around the centroid (irregularity factor). Free-flowing materials will give a dense pattern (small irregularity factor), close to the origin of the axes (frequent avalanches). The link between the granule size distribution of each of these samples and their flow avalanching behavior is shown in Figure 7b. Flow improves with increasingly bigger granule size, but as the fines almost disappear, the flow of the corresponding sample reverses back to less regular.

It is therefore concluded that a single parameter, the wet mass consistency, can be used to describe a wet mass and the dry granules that will ultimately be generated from it. In this case study of five formulations, it is clearly unnecessary to carry on wet massing beyond the 0.08 Nm consistency value for the lactose-based formulations or 0.12 Nm for the 'C' formulation, as further addition will only lengthen the drying process but not significantly modify the dry granule properties. Hence, the optimal dry granules

should be probed among the batches with consistencies in the 0.02−0.08 and 0.02−0.12 Nm ranges, respectively.

In conclusion, this work has shown that the wet mass consistency, as determined by mixer torque rheometry, is an essential parameter in the development of pharmaceutical wet granulation processes. It links the 'wet' and 'dry' stages of the operation, in terms of downstream production of dry granules of reproducible, optimized properties. This finding also reinforces the strategy of the scaleup methodology presented in the *Introduction* of this paper; that is, the transfer of a wet granulation process to a different manufacturing scale should require the reproduction of the same wet mass consistency and bulk density. In addition, this work suggests that some changes in the formulation can lead to the modification of the dimensionless power relationship. This suggestion was particularly evident when the filler was changed from a soluble to an insoluble hydrophilic material. Although for the limited range examined particle size and binder composition appeared not to be critical factors, in practice, the prediction of the target endpoint power consumption will only be reasonable if the dimensionless power relationship specific to the formulation studied is employed. The individual behavior of the materials is not able to be summed up to predict the wet massing behavior of a mixture of these materials, as demonstrated for the case of the 'D' formulation.

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