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High Shear Mixing Granulation of Ibuprofen and β-Cyclodextrin: Effects of Process Variables on Ibuprofen Dissolution

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ABSTRACT

The aims of the study were to evaluate the effect of high shear mixer (HSM) granulation process parameters and scale-up on wet mass consistency and granulation characteristics. A mixer torque rheometer (MTR) was employed to evaluate the granulating solvents used (water, isopropanol, and 1:1 vol/vol mixture of both) based on the wet mass consistency. Gral 25 and mini-HSM were used for the granulation. The MTR study showed that the water significantly enhanced the beta-cyclodextrin (βCD) binding tendency and the strength of liquid bridges formed between the particles, whereas the isopropanol/water mixture yielded more suitable agglomerates. Mini-HSM granulation with the isopropanol/water mixture (1:1 vol/vol) showed a reduction in the extent of torque value rise by increasing the impeller speed as a result of more breakdown of agglomerates than coalescence. In contrast, increasing the impeller speed of the Gral 25 resulted in higher torque readings, larger granule size, and consequently, slower dissolution. This was due to a remarkable rise in temperature during Gral granulation that reduced the isopropanol/water ratio in the granulating solvent as a result of evaporation and consequently increased the βCD binding strength. In general, the HSM granulation retarded ibuprofen dissolution compared with the physical mixture because of densification and agglomeration. However, a successful HSM granulation scale-up was not achieved due to the difference in the solvent mixture's effect from 1 scale to the other.

KEYWORDS: Granulation, ibuprofen, beta-cyclodextrin, complexation, dissolution.

INTRODUCTION

Beta-cyclodextrin (βCD) and its derivatives are cyclic oligosaccharide, formed of 7 glucopyranose units, known to form inclusion complexes with many kinds of drugs. The complexes have been used to improve solubility,[1] dissolution,[2] bioavailability,[3,4] and stability of poorly water-soluble drugs.[5]

The use of βCD as an excipient in directly compressible tablet formulations has been investigated in various studies.[6-8] The effect of cyclodextrin's water content on the crushing strength of tablets has been examined by Giordano et al.[9] However, only a few studies have reported on the use of βCD as a wet granulation excipient and on the effect of granulation processes on the dissolution of drugs granulated with βCD.[10] Shangraw et al[10] found that a granulated complex of βCD and progesterone formed harder tablets than a granulated physical mixture did, but comparable progesterone dissolution was obtained.

Wet granulation of ibuprofen (IBU) with βCD has been reported previously to enhance IBU's dissolution from tablets[11] and also improve its bioavailability.[12] However, in the studies, a low-shear granulation was done on a laboratory scale, and no granulation equipment type or process parameters were examined. Gainotti et al[13] have prepared IBU-βCD pellets by layering a powder or a solution of the drug on a pelletized mixture of microcrystalline cellulose (MCC) and βCD using a high shear mixer (HSM). Both processes showed enhancement in the dissolution of IBU from the pellets compared with a physical mixture of IBU, βCD, and MCC because of IBU-βCD complex formation. However, pellets prepared by the solution-layering technique showed a markedly faster dissolution than those prepared by the drug layering method because of a higher amorphous IBU content in the former. Although its cause was not mentioned in the report, the amorphousness was possibly due to more complexation that formed in the solution used for the layering.

Wet granulation is a size enlargement process that results in granules with different final characteristics depending on the equipment type, size, and process parameters. For example, HSM granulation usually results in more spherical, better-compacted granules with a wider particle size distribution than does fluid bed granulation, whose resulting granules often have a rough surface, lower density, and narrower particle size distribution.[14]

Several studies have addressed granulation in HSM granulators.[15,16] In HSM granulation, varying the liquid-to-solid ratio,[17] impeller speed,[18,19] binder flow rate,[19] and wet massing

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time[20] has been reported to affect the granules and consequently the tablet characteristics. However, scale-up of wet granulation is a crucial step necessary for the successful development and launching of drug products. Therefore, variations encountered during scale-up of HSM granulation do not allow for a direct extrapolation of the large-scale process conditions using lab scale parameters, as that usually results in inconsistency in the pharmaceutical properties of the final product. Several approaches have been studied and reported in the literature for the development of a successful scale-up process. Some of the approaches examined the influence of the tip speed,[21,22] relative swept volume,[23] and use of dimensionless numbers[24,25] (eg, power number, Reynolds number, and Froude number) for the estimation of the end point of granulation using power consumption. Ameye et al[26] showed that scale-up of wet granulation from a Mi-Pro 250 mixer up to Gral 10 could be achieved by adjusting the tip speed and water content. The authors used α-lactose monohydrate 200 M as the diluent and aqueous polyvinylpyrrolidone K-30 as the binder. Neither of the 2 excipients is known to have unusual binding tendencies that could modify scale-up. Therefore, the aim of this study was to investigate the effect of HSM granulation process parameters and scale-up on wet mass consistency and granulation characteristics of IBU and βCD.

Materials and Methods

Materials

βCD was obtained from Amaizo (Hammond, IN), IBU was from Albemarle Co (Baton Rouge, LA), and magnesium stearate was from Mallinckrodt Specialty Chemicals (St Louis, MO). All other chemicals used were of reagent grade.

Methods

Granulation and Preparation of Tablets

Granulation was done using high shear mixing. Prior to the high shear mixing process, a wet mass consistency study was employed using a Caleva mixer torque rheometer (MTR) (604600 model, Caleva Process Solutions Limited, Dorset, UK). This was done to determine the suitability of using the solvents (water and isopropanol) that were previously reported in the lab scale study[11] and examine the effect of a mixture of the 2 solvents (in a ratio of 1:1 vol/vol) on the rheology of the wetted mass. Initially, a steady baseline torque value was generated by running the torque mixer empty for a short period (30 seconds). A blend of IBU and βCD (35 g) in 2:1 molar ratio was added, and the mixer was then run for another 30 seconds, followed by addition of 0.5 mL of the solvent every 30 seconds (multiple solvent addition experiment). The recorded resistance of the sample to the shearing effect of the MTR contra-rotating blades provided the mean torque value that consequently determined the consistency of the wet mass.

A small laboratory-scale HSM granulator (Mi-pro, Pro-C-epT, Zelzate, Belgium) was first used. This was an attempt to predict the outcomes of granulation in a higher–shear capacity mixer, Collette Gral 25 (Machines Collette, Antwerp, Belgium), with its different process variables (eg, mixing time, solvent amount and type). The laboratory-scale HSM granulation was performed using a 1-L-capacity bowl and 13.8-cm mixer blade. Two minutes of dry mixing of IBU and βCD (250 g in a molar ratio 2:1) was performed prior to the addition of granulating solvent (37.5 mL) and was followed by 1 minute of mixing postaddition. The volume of granulating solvent used in this study was based on the ratio of the volume of solvent to the weight of solid used in the previously reported laboratory-scale granulation.[11] A physical mixture of IBU and βCD in the same molar ratio used for the granulations, was prepared by dry blending the 2 components in the mini-HSM for 2 minutes using the high impeller speed.

The mini-HSM was equipped with a strain gauge and infrared probe to monitor the torque reading and the wet mass temperature, respectively. The effects of 3 variables (solvent type, impeller speed, and spraying rate) on granulation were studied using a 2^3 full factorial experiment design (Table 1). The amount of granulating solvent used was 37.5 and 34.19 g for water and the isopropanol/water mixture, respectively. The amounts represented 13.0% and 12.0% wt/wt of the solid wet mass for each of the above 2 solvents, respectively. The impeller tip speed, which is reported to be directly related to the shear rate exerted by the impeller,[27] was calculated using Equation 1:

$$Tip\ speed = \frac{\pi ND}{t} \quad (1)$$

where N is the rpm of the impeller, D is the diameter of the impeller, and t is the time.

The dimensionless Froude number (Fr), a ratio of centrifugal force to gravitation force (a criterion used for dynamic similarities between mixers), was calculated using Equation 2:

$$Fr = \frac{N^2 D}{g} \quad (2)$$

where N represents the impeller number of revolutions per minute, D the diameter of the impeller, and g the gravitational constant.[23]

The granules were screened through Comil (Quadro Comil 197S, Quadro Engineering Inc, Ontario, Canada) with a 0.075″ pore size screen, dried at 60°C for 2 hours, mixed with 1%

Table 1. 2^3 Full Factorial Design of the Mini–High Shear Mixer Experiments and the Physical Properties of Prepared Granules and Tablets (mean ± SD)

Solvent	Spraying Rate (mL/min)	Impeller Speed (rpm)	Geometric Mean Particle Size (μm)	Carr's Index	Hardness (kp)
Water	2.5	1000	107.7 ± 4.0	31.0 ± 1.0	16.6 ± 3.4
		600	175.1 ± 3.1	33.8 ± 2.2	20.9 ± 1.0
	1.8	1000	149.6 ± 3.3	30.0 ± 1.6	20.9 ± 0.4
		600	122.9 ± 4.0	33.2 ± 2.5	19.2 ± 0.4
Isopropanol/water (1:1)	2.5	1000	231.0 ± 2.1	32.8 ± 0.7	18.4 ± 1.1
		600	409.4 ± 2.1	25.3 ± 1.3	20.2 ± 1.8
	1.8	1000	332.6 ± 2.3	27.3 ± 2.5	19.5 ± 0.9
		600	401.7 ± 2.3	24.5 ± 1.8	17.5 ± 4.2

magnesium stearate, and compressed into 375-mg tablets using a Carver press (model C, Fred S. Carver Inc, Menomonee Falls, WI) at a compression force of 5000 lbf (~22.0 kN), with a concave B tooling punch and 3/8-inch inner diameter die.

The Gral 25 granulation was performed using a batch size of 6 kg. Power consumption and temperature (measured using a noncontact thermometer) were recorded during dry mixing and used later as a baseline to calculate the change in power consumption and temperature (ΔP and ΔT, respectively) during granulation. An amount of 820 g ± 0.5% of a granulating solvent mixture of isopropanol and water in the ratio of 1:1 vol/vol was used. This amount of the solvent represented 12.0% wt/wt of the solid wet mass, a percentage similar to that used for the same solvent in the mini-HSM experiments.

During granulation, the chopper was allowed to run at a constant speed of 3000 rpm, and the power consumption and blend temperature were recorded every 30 seconds. One minute of blending was allowed after complete solvent addition. The wet mass was passed through Comil with the same specifications used for the mini-HSM batches. The granules were then oven-dried at 60°C for 2 hours, screened, and mixed with 1% magnesium stearate in a 16-quart V blender (LB-4468 model, Patterson-Kelly Co, East Stroudsburg, PA) for 5 minutes.

Table 2 shows the 2 × 2 full factorial experimental design used to evaluate the effect of varying the impeller speed and spraying rate on granulation. The tip speed and Froude number were calculated for each impeller speed using Equations 1 and 2, respectively.

Characterization of Granules

Sieve analysis for 100 g of granules was conducted using a set of nested sieves (mesh sizes #20, 30, 40, 60, 80, 120, 170, 270, and 400, which correspond to pore sizes 850, 600, 425, 250, 180, 125, 90, 53, and 38 μm, respectively). The geometric mean particle size was calculated from a log-probability plot of particle size vs percent cumulative weight undersize.

Bulk and tap density of granules and the physical mixture (mixed in HSM and oven-dried) were determined after 500 taps using a Vander Kamp Tap Density tester (10705 model, Van Kel Industries, Edison, NJ). Carr's index was calculated using Equation 3:

$$Carr's\ index = \frac{Tap\ density - Bulk\ density}{Tap\ density} \times 100 \quad (3)$$

A Computrac Max 2000 moisture analyzer (Arizona Instruments LLC, Tempe, AZ) was used to measure loss on drying of granules and physical mixture samples (1.0 g ± 0.2).

Characterization of Tablets

The crushing strength, diameter, and thickness of tablets were measured using an Eliza Test 3+ Vision Tablet Testing System (Elizabeth-Hata International, North Huntingdon, PA).

Table 2. 2^2 Full Factorial Design for the Gral 25 Experiments and the Physical Properties of Prepared Granules and Tablets (mean ± SD)

Spraying Rate (mL/min)	Impeller Speed (rpm)	Geometric Mean Particle Size (μm)	Carr's Index	Weight (g)	Hardness (kp)
60	440	268.5 ± 2.2	30.8 ± 0.6	366.4 ± 9.9	20.4 ± 2.1
	295	124.3 ± 2.3	22.8 ± 1.4	377.2 ± 2.5	17.2 ± 1.1
43	440	310.3 ± 2.0	33.1 ± 0.6	371.2 ± 7.3	19.5 ± 2.6
	295	160.6 ± 2.2	27.5 ± 0.3	375.6 ± 3.5	18.5 ± 1.1

A Philips X-ray diffractometer (PW-3710 model, Philips, Almelo, Holland), with PW 3710 scanner/PW 1830 generator and a Cu k α anode, was used for the analysis. X-ray diffraction patterns of tablets lightly milled in a mortar were determined between $2\theta = 5°$ and 35° at 40 kV, 30 mA, and a scanning speed of 1.5°/min.

The dissolution study was performed using a US Pharmacopeia Type 2 apparatus (VanKel Industries) with the stirring speed of paddles set at 100 rpm. Six tablets from each batch were placed in 900 mL of a dissolution medium consisting of phosphate buffer (pH 6.5, 37°C). Samples taken at different time intervals were filtered through 5-μm nylon filter membrane needles and analyzed for IBU using a high-performance liquid chromatography (HPLC) assay.[11] Briefly, the 1-mL samples were filtered and analyzed on a Shimadzu HPLC system (Shimadzu Scientific Instruments, Columbia, MD) after extraction with isooctane/isopropanol. The percentage of IBU released from tablets during dissolution was calculated based on the mean drug content determined for each batch.

Results and Discussion

MTR

A substantial rise in torque (up to 3.3 Nm) occurred with the addition of water as a granulating solvent (Figure 1). This is a reflection of the high binding effect of βCD resulting from the hydrophilic outer surface of βCD.[9,28] The cyclodextrin dissolved partially in water and increased the viscosity of the binder solution, causing coalescence of particles and formation of large agglomerates. In contrast, isopropanol did not cause any remarkable increase in torque; instead, it caused a direct transformation of the blend from powder to slurry. This is due to its relatively lower polarity and formation of weaker interparticle liquid bridges.

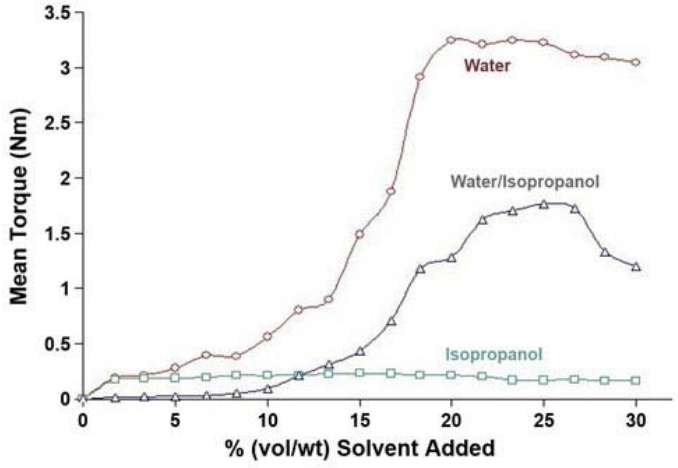

Figure 1. Effect of granulating solvent on the mean torque measurements obtained with ibuprofen–beta-cyclodextrin mixture in a Caleva mixer torque rheometer.

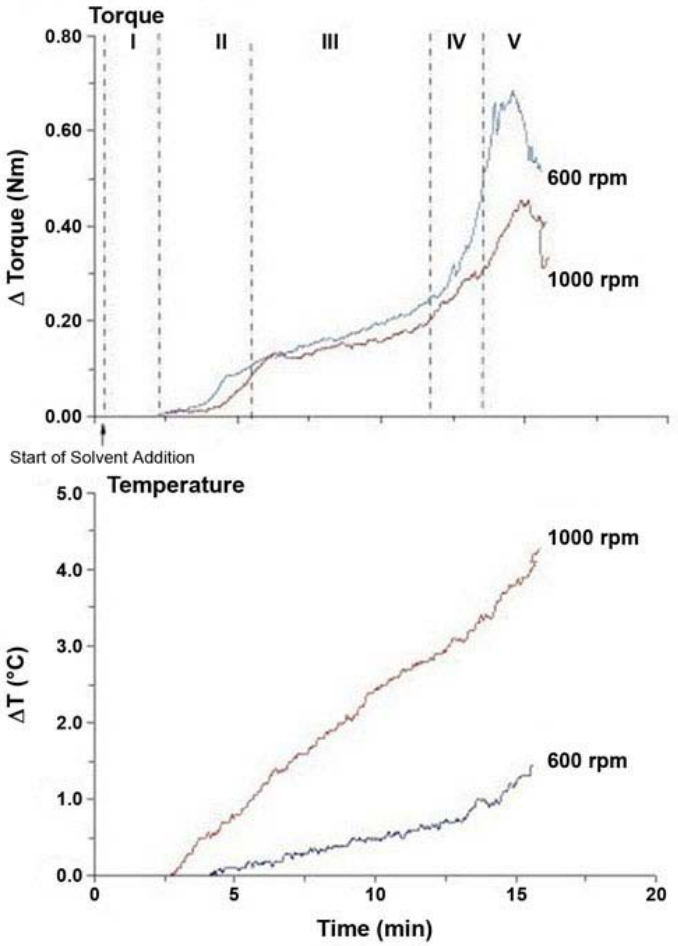

Figure 2. Effect of impeller speed on changes in torque reading and temperature during mini–high shear mixer granulation with isopropanol/water mixture added at a spraying rate of 2.5 mL/min.

The use of a 50% vol/vol mixture of water and isopropanol produced an intermediate torque value of ~1.7 Nm.

Mini-HSM Granulation

On the basis of the MTR results, water and the isopropanol/water mixture were the only solvents used for this study. Mini-HSM granulation with water and the isopropanol/water mixture showed torque profiles similar to that observed with the MTR (data not shown). The granulation with water caused a tremendous increase in torque with heavy fluctuation, which made continuation of some of the granulations impractical. Therefore, the isopropanol/water mixture was the only solvent selected for further studies on the Gral 25 HSM.

The 5 stages of granulation reported by Leuenberger[29] and Shiraishi et al[30] are depicted in Figure 2. Phases I to III included wetting of the particles, formation of weak liquid

bridges, and relative increase in strength or nucleation. After phase III, as more liquid was added, the strength of the bridges increased drastically, leading to the high rise in torque. At this stage, 2 opposing forces (breaking and coalescence) acted on the particles. Breaking force resulted from impact on granules against the walls of the bowl and the blades of the impeller, whereas coalescence force developed from the collision of granules with each other.[18] Coalescence of the colliding particles occurred because of dissipation of the kinetic energy of collision by the flow of the binder solution between the particles to form liquid bridges[31] and by the plastic deformation of the colliding granules.[32] Therefore, the strength of the liquid bridges occurring within the agglomerates was determined by the extent of granule breakage and/or coalescence.[33]

Torque and Temperature Measurements

During the first 3 phases of isopropanol/water mixture granulation, the impeller speed did not remarkably affect the torque (Figure 2A). In the fourth granulation phase, the high impeller speed caused an unexpectedly lower torque. The presence of isopropanol in the solvent mixture may have weakened the strength of interparticle liquid bridges to the extent that the breaking force was greater than the coalescence force.

The rise in temperature during the mini-HSM granulation was very small (<5°C), but the higher impeller speed caused a greater temperature increase than the lower speed did (Figure 2B). This was attributed to coalescence, as explained earlier.

The lower spraying rate resulted in slightly higher torque readings because of the longer wet massing time, which caused more densification to the granules (data not shown). However, there was no remarkable difference in the temperature rise observed between the 2 spraying rates.

Characterization of Granules

A similar percent loss on drying, ranging between 4.5% and 5%, was observed for all the batches, with no remarkable differences seen between the granulations.

Mini-HSM–prepared granules showed high geometric mean particle size because of coalescence and agglomeration of particles during granulation. Granules prepared using water showed a lower geometric mean particle size than did granules from the isopropanol/water batches (Table 1). This was due to the very hard large agglomerates formed during granulation with water, which upon milling formed smaller particles and caused faster dissolution than did granules made using the isopropanol/water mixture.

The high impeller speed resulted in granules with smaller particles (Table 1). As explained earlier, this was due to weakening of the liquid bridges between particles.

Granulation with the isopropanol/water mixture produced granules with a Carr's index lower than that of the water-prepared granules, which indicated a relatively better flow for the isopropanol/water granules (Table 1). Decreasing the impeller speed yielded particles with a lower Carr's index. The larger particles obtained by the low impeller speed allowed for higher intergranular porosity after tapping, resulting in smaller differences between bulk and tap density. Consequently, a lower Carr's index was observed at the low impeller speed than at the high impeller speed.

Characterization of Tablets

The crushing strength of tablets compressed from mini-HSM–prepared granules was in the range of 16.6 to 20.9 kp (Table 1). However, no differences in hardness were associated with solvent type or process parameter variation.

The drug content of tablets compressed from mini-HSM batches was in the range of 95% to 110%. Tablets prepared using mini-HSM granules showed slower dissolution than did tablets prepared from the oven-dried physical mixture, because of the highly densified larger particles obtained by the mini-HSM granulation (Figure 3). Tablets prepared using the isopropanol/water mixture showed slower release than did tablets of the water-prepared batches, which might have been due to the larger particle size of the granules prepared

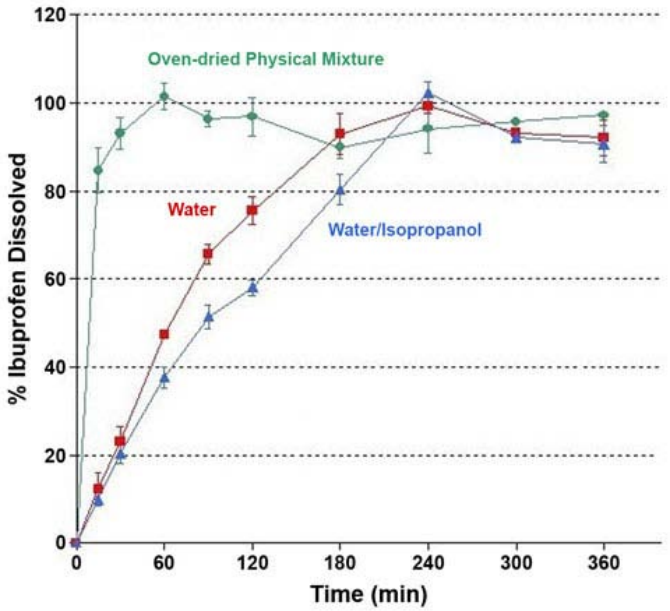

Figure 3. Dissolution of tableted mini–high shear mixer granules prepared using different solvents (impeller speed = 1000 rpm, spraying rate = 2.5 mL/min).

using the isopropanol/water mixture. Varying the impeller speed (Figure 4) or the spraying rate (data not shown) did not significantly affect the release of IBU from tablets, regardless of the granulating solvent used ($P < .05$).

Gral 25 HSM

Power Consumption and Temperature

During Gral 25 granulation, the use of high impeller speed caused a sharp rise in power consumption (Figure 5A). This increase in power consumption was accompanied by a rise in temperature, which was greater for the higher impeller speed (>35°C) than for the lower one (<20°C) (Figure 5B). This difference was due to the greater energy input by the higher speed, which was converted into heat because of friction between the agglomerates and the blades of the impeller.

A higher rise in temperature was observed for the lower spraying rate because of the longer massing time. However, no difference in the power consumption change (Δ power) was observed (data not shown).

Characterization of Granules

The moisture content of all the granules after drying was in the range of 5.5% to 6.5%.

The impeller speed was found to greatly affect the granule particle size. Using a higher impeller speed while maintaining a constant spraying rate produced granules with a larger geometric mean particle size (Table 2). On the other hand, lowering the spraying rate resulted in larger granules because of the longer massing time required.

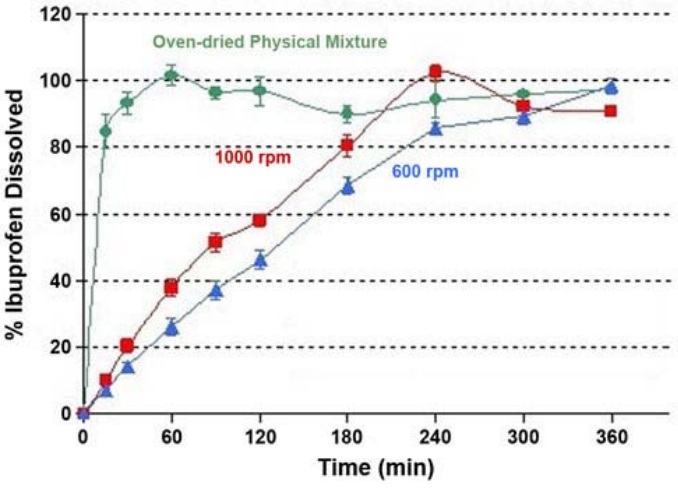

Figure 4. Effect of impeller speed on dissolution of tableted mini–high shear mixer granules prepared using isopropanol/water mixture (spraying rate = 2.5 mL/min).

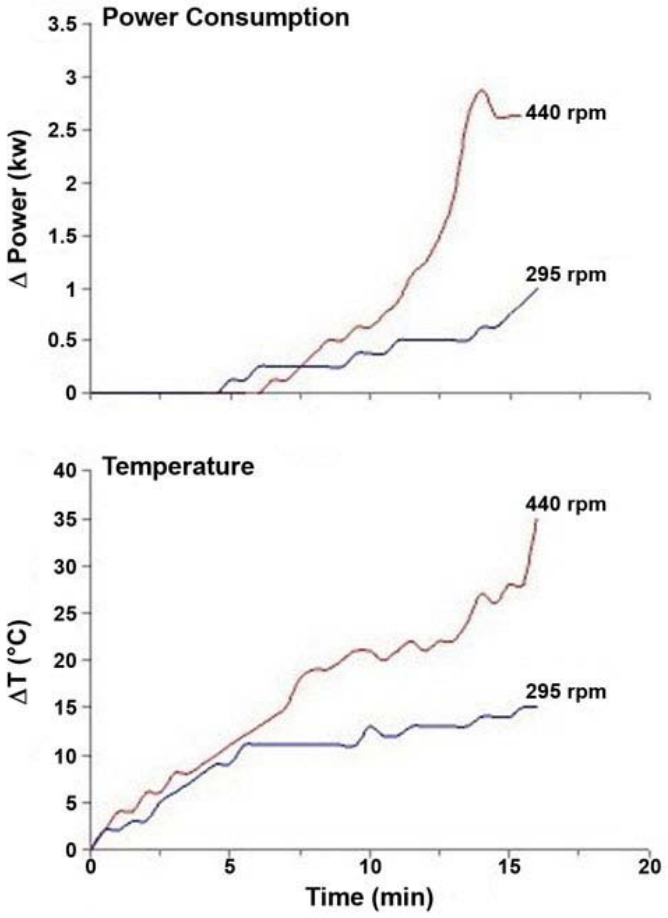

Figure 5. Effect of impeller speed on changes in power consumption and temperature during Gral 25 granulation with isopropanol/water mixture (1:1 vol/vol) added at a spraying rate of 43 mL/min.

The larger particle size obtained by raising the impeller speed was accompanied by an increase in the Carr's index, which is indicative of poor flow. The spray rate did not affect the Carr's index.

Characterization of Tablets

The use of the Gral high impeller speed increased the tablet weight standard deviation (Table 2), perhaps because the larger particle size and higher Carr's index of the high-speed granulation resulted in an erratic powder flow during compression.

As shown in Table 2, varying the impeller speed and/or the spraying rate during granulation did not have a significant impact on tablet crushing strength.

To evaluate whether the process affected the crystallinity of the components, diffraction patterns of crushed tablets were studied. Typical X-ray diffraction profiles of tablets prepared from the Gral 25 granulation were almost similar to

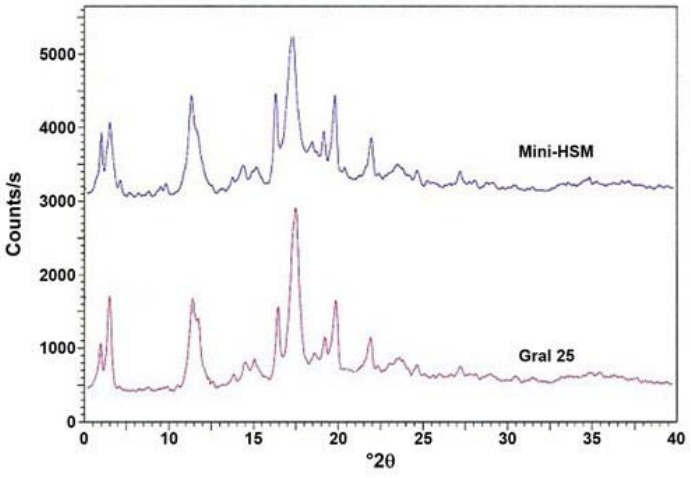

Figure 6. X-ray diffraction patterns of tablets compressed from mini-HSM and Gral 25 granules. HSM indicates high shear mixer.

those of the mini-HSM (Figure 6), indicating that there was no marked difference in the crystalline characteristics of the 2 granulations.

Some of the Gral-prepared granules were compressed on a Carver press at a compression force of 22.0 kN, which was comparable to that used for the mini-HSM granules. The dissolution of the resulting tablets was similar to that of the mini-HSM tablets, where granulation resulted in slower dissolution than for the oven-dried physical mixture, but impeller speed and spraying rate did not significantly influence dissolution (data not shown). The lack of effect of impellar speed and spraying rate on dissolution could be a result of the higher compression force and longer dual time of the Carver press, which might have overcome the effect of impeller speed on dissolution.

Some granules were compressed on a Hata press at 9.8 kN, which was a more workable and practical compression force. Significant retardation in dissolution by increasing the impeller speed ($P < .05$) was observed (Figure 7). This result might have been due to the more densified larger granules obtained by the high impeller speed. In contrast, the spraying rate had no significant influence on dissolution for the Hata-compressed tablets (data not shown).

Scale-up and Comparison of Mini-HSM and Gral 25

Both mixers have the same ratios of bowl diameter to bowl height and bowl diameter to impeller diameter (1.4 and 1.0, respectively). Therefore, to attain comparable kinematic and dynamic similarities between the 2 pieces of equipment, the impeller speed of the mini-HSM was adjusted (based on the Gral 25 speeds) and the corresponding tip speeds and Froude numbers were calculated accordingly. The corresponding tip speeds for the 600 and 1000 rpm impeller speeds of the mini-

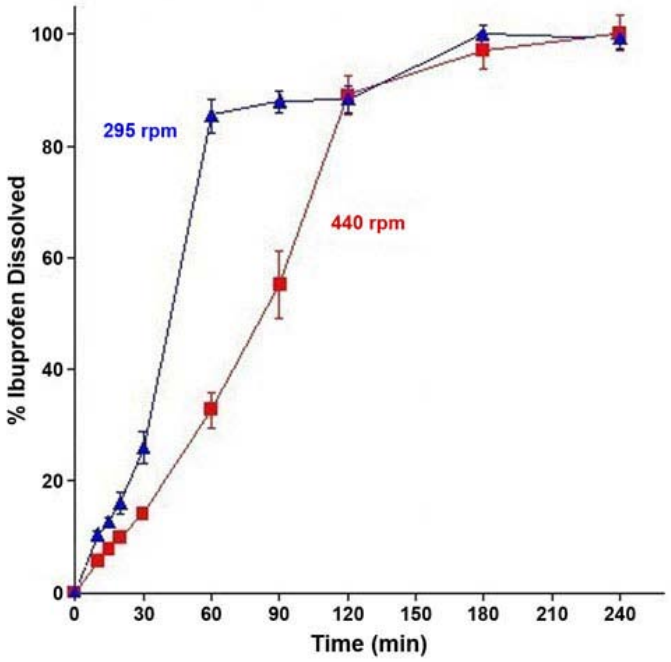

Figure 7. Dissolution of Hata press–compressed tablets of Gral 25 granulations prepared using different impeller speeds at a spraying rate of 60 mL/min.

HSM were 4.31 and 7.2 m/s, respectively, while their Froude numbers were 1.4 and 3.9, respectively. The Gral 25 tip speeds and Froude numbers for the 295 and 440 rpm impeller speeds were 5.6 and 8.4 m/s, and 0.9 and 2.0, respectively (Table 3). The 2 mixers showed geometric similarities. Although the values for the tip speed and Froude number were slightly different for the 2 granulators, the magnitude of the difference between the 2 impeller speeds of the same granulator was comparable.

For scale-up purposes, a fair comparison of the effect of process variables on granulation for the 2 granulators could be obtained. However, formulation variables or process output can modify or hinder scale-up, as shown in this study. The temperature rise during the Gral 25 granulation was

Table 3. Geometric Similarity, Tip Speeds, and Froude Numbers of the Impeller Speeds Used for the 2 High Shear Mixer Granulators

Granulator	Mini–High Shear Mixer		Gral 25	
Impeller diameter (*I*) (cm)	13.8		36.0	
Bowl diameter (*B*)(cm)	14.2		37.5	
Bowl height (*h*)(cm)	10.0		26.5	
B/h	1.4		1.4	
B/I	1.0		1.0	
Impeller speeds (rpm)	600	1000	295	440
Tip speed (m/s)	4.3	7.2	5.6	8.4
Froude number	1.4	3.9	0.9	2.0

more than 30°C, while for the mini-HSM it was only 5°C. This large difference in temperature elevation between the 2 granulators was due to the more effective conversion of energy into heat by the heavier mass present in the larger Gral equipment.[34] This variation might explain the different effect of impeller speed on torque and power consumption readings of the mini-HSM (Figure 2A) and the Gral (Figure 5A).

The high rise in temperature during the Gral granulation, especially with the high impeller speed, caused more evaporation of isopropanol (boiling point 82°C) from the solvent mixture than from water. This might have shifted the ratio of isopropanol and water in the solvent mixture to favor the presence of more water in the granulation matrix. Consequently, much stronger liquid bridges were formed between the Gral agglomerates than between the mini-HSM's. Therefore, more coalescence between granules took place with the Gral, instead of the breaking force acting on the granules from the impeller during the mini-HSM granulation, coalescence between granules took place during the Gral 25 granulation. The consequence was formation of weaker liquid bridges between particles in the former process. This difference in the effect of the impeller speed on particle agglomeration could also explain the higher geometric mean particle size of granules obtained by increasing the Gral impeller speed, whereas increasing the speed on the mini-HSM reduced the size of the granules.

Considering the variables used in the study, scale-up of HSM granulation from Mi-pro to Gral 25 could not be obtained. This contradicted the results of Ameye et al,[26] who showed a possible scale-up from the lab-scale Mi-Pro to Gral 10. The differing result could be explained by the fact that water was the only granulating solvent component used by Ameye et al. Thus, in their study the possibility of a change in the composition of the solvent because of evaporation by scale-up from the Mi-pro to Gral was negligible, but this phenomenon was encountered in our study with the use of a solvent mixture of isopropanol and water. In addition, the scale-up characteristics from Mi-pro to Gral 10 that Ameye et al[26] reported may not be applicable to scale-up to Gral 25. Moreover, as noted above, the authors used lactose monohydrate and polyvinylpyrrolidone instead of βCD, which caused significant intergranular binding.

CONCLUSIONS

The use of water and βCD in granulation should be carefully considered because of the high binding tendency of βCD. The heat generated during large-scale HSM granulation could also influence the ratio of a granulating solvent mixture containing a volatile component. The effect of heat on granulating solvent composition in a manufacturing setting scale up could become significant, affecting the mixing process.

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