Drug Development and Industrial Pharmacy, 22(9&10), 917-924 (1996)

Alternative Granulation Technique: Melt Granulation

Alan Royce,[1] Jiwaji Suryawanshi,[1] Udayan Shah,[2] and Krishna Vishnupad[1]

[1]*Drug Delivery Systems, Technical R&D, Sandoz Research Institute, Sandoz Pharmaceuticals Corp., 59 Route 10, E. Hanover, New Jersey 07936-1080*
[2]*Warner Lambert Co., 400 W. Lincoln Ave., Lititz, Pennsylvania 17543*

INTRODUCTION

A melt granulation process has been investigated (1,2) which efficiently agglomerates pharmaceutical powders for use in both immediate- and sustained-release solid dosage forms. The process utilizes materials that are effective as granulating fluids when they are in the molten state. Cooling of the agglomerated powders and the resultant solidification of the molten materials completes the granulation process. Both the molten agglomeration and cooling solidification were accomplished in a high shear Collette Gral mixer equipped with a jacketed bowl. Hence, the melt granulation process replaces the conventional granulation and drying operations which use water or alcohol solutions. The melt granulation process has been investigated using immediate- and sustained-release TAVIST® (clemastine fumarate USP) tablet formulations. The TAVIST granulations have been characterized by power consumption monitoring, measurement of the granulation particle size distribution, bulk and tapped density determinations, and loss-on-drying measurements. Scale-up of the melt granulation process for the sustained release TAVIST tablet formulation was judged successful based on a comparison of the hardness, friability, weight uniformity during compression, disintegration time, and dissolution rate data obtained at different manufacturing scales.

MATERIALS

Evaluated as melt granulation materials were: glycerylpalmitostearate (Precirol ATO-5, Gattefosse, Westwood, NJ) with a melting point range of 52°–55°C, polyethylene glycol 8000 NF (Carbowax 8000, Union Carbide Corp., Danbury, CT) with a melting point range of 60°–63°C, and paraffin NF (Ruger Chemical Co., Irvington, NJ) with a melting point range of 47°–65°C.

The tablet diluents consisted of anhydrous lactose NF (Direct Tableting, Sheffield Products, Norwich, NY), pregelatinized starch NF (Starch 1500, Colorcon, West Point, PA), and hydroxypropyl methylcellulose USP 2208 (Methocel K15M, Dow Chemical Co., Midland MI).

Povidone USP (Kollidon K-30, BASF, Parsippany, NJ) was the binder used in the tablets manufactured by conventional granulation. Crospovidone NF (Polyplasdone XL, ISP, Wayne, NJ) was used as a tablet disintegrant in the immediate-release tablet formulations.

Colloidal silicon dioxide NF (Cab-O-Sil, Amorphous Fumed Silica M5, Cabot, Corp., Tuscola, IL) was used to improve powder flow, and talc USP (hydrous magnesium silicate, Luzenac America, Alpine, AL) was used as an antiadherent. Stearic acid NF (Hystrene 5016 NF, Humko Chemical, Witco Corp., Newark, NJ) was the tablet lubricant in all of the formulations.

TAVIST drug substance was obtained from Sandoz Pharma Ltd., Basel, Switzerland.

METHODS

Formulations

The sustained-release TAVIST tablet formulations are presented in Table 1. In these formulations, glycerylpalmitostearate (water insoluble) and polyethylene glycol 8000 (water soluble) were used as the melt granulating materials in various combinations. Lactose and hydroxypropyl methylcellulose comprised the bulk of the formulation. Sustained-release properties were imparted to these formulations by the hydroxypropyl methylcellulose, which is known to form a hydrophilic gel matrix in an aqueous environment (3).

In one series of experiments with the lactose–hydroxypropyl methylcellulose formulations, the concentration of glycerylpalmitostearate was varied from 0% to 15% w/w (based on the total amount of the formula components), while keeping the concentration of polyethylene glycol constant at 10% w/w. In another experiment, 15% w/w glycerylpalmitostearate was used with 15% w/w polyethylene glycol 8000. The total concentrations of molten granulating materials evaluated were: 10%, 15%, 20%, and 30% w/w.

Table 1

Sustained Release TAVIST Tablet[a] Formulations: Melt Granulation

Ingredient	%/Unit
Clemastine fumarate USP	1.5
Lactose NF, anhydrous[b]	33–53
Hydroxypropyl methylcellulose USP, 2208[c]	30
Glycerylpalmitostearate[d]	≤15
Polyethylene glycol NF, 8000	10–15
Talc USP	3
Colloidal silicon dioxide NF	0.5
Stearic acid NF	2

[a]Total tablet weight 180 mg.
[b]Direct tableting grade.
[c]Methocel K15M.
[d]Precirol ATO5 grade.

The immediate-release TAVIST tablet formulations prepared by the melt granulation process are shown in Table 2. In these formulations, three different molten granulating materials were evaluated: glycerylplamitostearate, polyethylene glycol 8000, and paraffin.

Starch and lactose were used as the main diluents in these formulations. In these starch–lactose formulations, glycerylpalmitostearate was evaluated alone at a 30%

Table 2

Immediate-Release TAVIST Tablet[a] Formulations: Melt Granulation

Ingredient	%/Unit
Clemastine fumarate USP	1.5
Lactose NF, anhydrous[b]	30
Pregelatinized starch NF[c]	30
Glycerylpalmitostearate[d]	0–30
Paraffin NF	0–15
Polyethylene glycol NF, 8000	0–30
Crospovidone NF[e]	3
Talc USP	3
Colloidal silicon dioxide NF	0.5
Stearic acid NF	2

[a]Total tablet weight 180 mg.
[b]Direct tableting grade.
[c]Starch 1500.
[d]Precirol ATO5 grade.
[e]Polyplasdone XL.

w/w level and at a 15% w/w level with 15% w/w polyethylene glycol 8000. Polyethylene glycol 8000 was also evaluated alone at a 30% w/w level and at a 15% w/w level with 15% w/w paraffin. The total concentration of these granulating materials was kept constant at 30% w/w.

Immediate-release TAVIST tablets prepared by a conventional wet granulation process were evaluated for comparison. In this formulation, starch and lactose were used as the main diluents, povidone functioned as the binder, crospovidone was added as the disintegrant, and purified water was used as the granulating agent. Colloidal silicon dioxide, talc, and stearic acid were added to the dried granules as an outer phase.

Melt Granulation

Prior to use, the glycerylpalmitostearate, polyethylene glycol 8000, and paraffin were passed through a No. 12-mesh screen. The required amount of the drug and lactose were placed in a 75-liter Collette Gral mixer and dry blended for 1 min at low speed using the plow only. The resulting mixture was further blended for 1 min at high speed using the plow only. The hydroxypropyl methylcellulose and granulating materials were added to the preblend and mixed for 1 min at low speed using the plow only. For the immediate-release formulations starch and crospovidone were added to the preblend in place of hydroxypropyl methylcellulose.

A 75-liter Collette Gral mixer was equipped with a jacketed bowl. A steam/water mixture was allowed to circulate in the jacket to increase the temperature of the blended ingredients contained in the bowl. Mixing at low plow speed was maintained during the heating cycle. At the melting point of the granulating materials, a molten liquid was formed which agglomerated the powder blend. The granulation end point was determined by measuring the power consumption of the mixer plow.

After reaching the granulation end point, the steam was discontinued and cold water was circulated in the jacketed bowl. During the cooling cycle, the product was continuously blended at a low plow speed.

When the product temperature was reduced to 50°C, the granulation was immediately passed through a No. 12-mesh screen using an oscillator. The immediate screening was required to prevent the hardening of the granulation. The sized granulation was transferred to a planetary mixer. The colloidal silicon dioxide, talc, and stearic acid were screened through a No. 60-mesh bolting cloth. The screened materials were then added to the planetary mixer and mixed for 5 min.

Conventional Granulation

A preblend of drug and lactose was prepared in the Collette Gral 75-liter mixer in a manner identical to that used for the molten granulated formulations. Starch, povidone, and crospovidone were added to the dry preblend and mixed for 1 min at low speed using the plow only. Purified water was added to the mixture while blending at slow plow speed to produce the granulation. The wet mass was dried in the fluid bed dryer and then screened through No. 12-mesh screen using an oscillator. Colloidal silicon dioxide, talc, and stearic acid were screened through a No. 60-mesh bolting cloth and added to the mixture as described for the melt granulations.

Evaluation of Granulation and Tablets

The granulation process was monitored using power consumption. A 75-liter Collette Gral high shear mixer (Machines Collette, Antwerp, Belgium) was fitted with an alternating current, three phase watt transducer (Model PC5-053B, Ohio Semitronics Inc., Columbus, OH) on the plow motor. The transducer was calibrated by the manufacturer for a 0–20 kW range for a current output of 0 to 1 mA.

The particle size distribution of the granulations before adding the outer phase, nongranulated components (colloidal silicon dioxide, talc, and stearic acid) was determined by sieve analysis. A geometric mean diameter (dg_{50}) and geometric standard deviation (σg) were determined graphically using a log-normal size distribution (4). The loss-on-drying of the granulation was determined by a Computrac moisture analyzer at 90°C. The bulk and tapped density values ($N = 100$ taps) were also determined for each blend.

Tablets were prepared on a Manesty Betapress. The tablets were evaluated for hardness, thickness, friability, disintegration time, and drug dissolution. The average tablet hardness of each formulation was determined using a Schleuniger 6d hardness tester, and 20 tablets were used to assess the friability of the tablet formulations using a Roche-type friabilator. A spectrophotometric method was used to evaluate the dissolution rate of the tablets in deionized water at 37°C using the USP paddle method at 50 rpm.

A sustained-release TAVIST 2-mg formulation was progressively scaled up into 150-liter and 300-liter Collette Gral mixers with jacketed bowls. The in-process and final release properties of the granulations and tablets were compared to evaluate the scale-up process.

RESULTS AND DISCUSSION

The granulation end point was determined for each formulation by measuring the power consumption (5). A typical power consumption profile obtained during the melt granulation process is presented in Fig. 1. The profile can be divided into seven phases. Phase 1 represents the mixing of lactose and TAVIST for 1 min at low speed (203 rpm) using the plow only. The constant and relatively low power consumed indicates no cohesion among the primary powder particles when blending them in a dry state at low shear. During phase 2, the power consumption increased to a new constant value since the speed of mixing was increased (306 rpm) for 1 min.

In phase 3 of the power consumption profile, additional dry materials were added to the bowl of the mixer and the low mixing speed was resumed. The slight rise in the power consumed is due to the additional material charged to the bowl. After mixing the dry powders for 2 min, the heating cycle was started. Within 3 min, the temperature of the jacketed bowl surface increased to the melting point of the granulating materials. At this point, a slow rise in the power consumed is observed, as shown in phase 4 of Fig. 1. In this phase, the molten liquid appears to be functioning as a traditional granulation liquid by forming liquid bridges between the primary powder particles (6). This cohesion among the particles increases the resistance towards mixing and an increase in the power consumption is observed (7).

After approximately 11 min of heating, the power consumption has reached a constant value, as phase 5 of the power consumption profile indicates. This level of power consumption indicates the end point of the melt granulation process. At this point, it is presumed that all of the granulating materials have melted and have reached a steady-state level of granule nucleation, consolidation, and coalescence. Within this same time frame, the rise in product temperature within the bowl has also started to level off. The constant power consumption at this stage and the lack of any evidence of ball growth suggests that the liquid bridges between primary particles formed by the molten granulating materials are relatively weak, and therefore consolidation of the agglomerates is limited (8).

After achieving the granulation end point, the heating was discontinued. The temperature of the hot mix was cooled by circulating cold water in the jacketed bowl. Mixing at low speed with the plow only was maintained during the cooling cycle as shown in phase 6 of the power consumption profile. A rise in the power consumed is observed in this phase and may be attributed to coalescence of the particles (9). The solidifying granulating material presumably increases the strength of the agglomerates and permits additional coalescence. Before adding the outer phase components (colloidal silicon dioxide, talc, and stearic acid), the cooled and sized granules were returned to the mixer and the power consumption was measured as indicated by phase 7 of the profile in Fig. 1. In this final phase of the profile, the cooled, sized granules are shown to have little cohesiveness which is important for further processing into solid dosage forms.

Figure 2 compares the power consumption profiles of a melt granulation versus a conventional wet granulation. In the initial dry mixing phases and during blending of the finished sized granules prior to the addition of the outer phase components (colloidal silicon dioxide, talc, and stearic acid), similar power consumption levels were obtained for both granulation processes. However, during the agglomeration phase, higher power

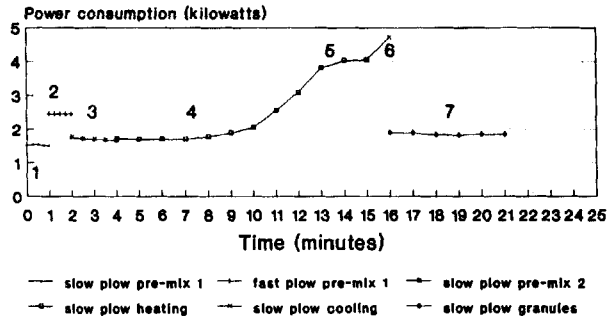

Figure 1. Melt granulation power consumption for lactose-starch formulation. Formulation containing 15% glycerylpalmitostearate and 15% polyethylene glycol 8000.

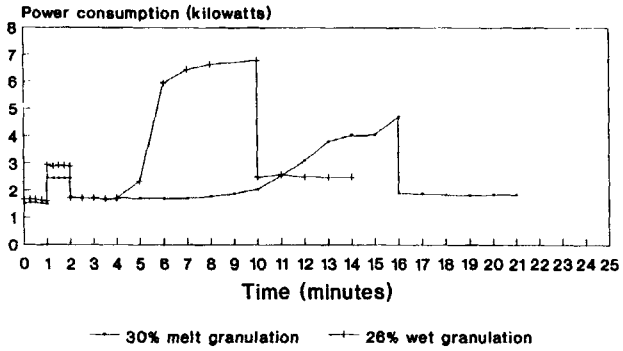

Figure 2. Power consumption for melt versus wet granulation of lactose-starch formula. Melt: 15% glycerylpalmitostearate, 15% PEG 8000. Wet: 5% PVP and 21% water.

levels were observed during the wet granulation versus melt granulation process. Geometric mean particle diameters (dg_{50}) of 380 and 490 μm were obtained for the melt and wet granulations, respectively.

The effects of varying amounts of molten granulating materials on the power consumption are shown in Fig. 3 for the lactose–hydroxypropyl methylcellulose sustained-release formulations. As shown, the lactose-hydroxylpropyl methylcellulose formulation containing 15% w/w glycerylpalmitostearate and 15% w/w polyethylene glycol 8000 displayed a higher peak value during the power consumption versus the formulation containing 10% w/w glycerylpalmitostearate and 10% w/w polyethylene glycol 8000. Increasing the amount of molten granulating material from 10% glycerylpalmitostearate and 10% polyethylene glycol 8000 to 15% w/w glycerylpalmitostearate and 15% w/w polyethylene glycol 8000 increased the dg_{50} values from 250 to 310 μm, respectively. Hence, for these granulations with a constant ratio of glycerylpalmitostearate to polyethylene glycol, an increase in the amount of molten material related to higher peak power consumption levels and larger geometric mean granule sizes.

The effect of the melt granulation process on the particle size distribution for the lactose–hydroxypropyl methylcellulose sustained-release formulation containing 15% w/w glycerylpalmitostearate and 15% w/w polyethylene glycol 8000 is presented in Fig. 4. As shown, prior to granulation a geometric mean diameter (dg_{50}) of 120 μm was found with a geometric standard deviation (σg) of 2.22 μm. After granulation, a dg_{50} of 310 μm with a σg of 1.90 μm was obtained.

As reported by other investigators (10), a correlation was observed for the total amount of molten granulating material with the granule particle size. Increasing

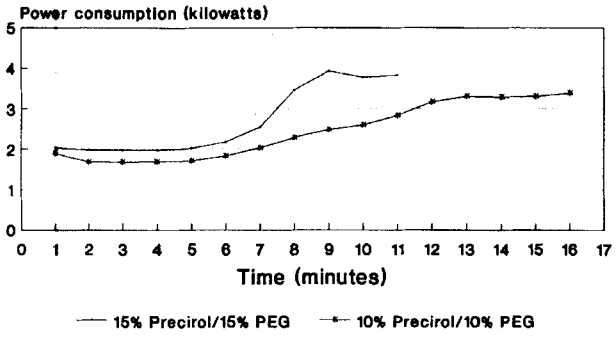

Figure 3. Power consumption during heating for 20% and 30% of molten materials. Glycerylpalmitostearate and polyethylene glycol 8000 in lactose–hydroxymethylcellulose formulations.

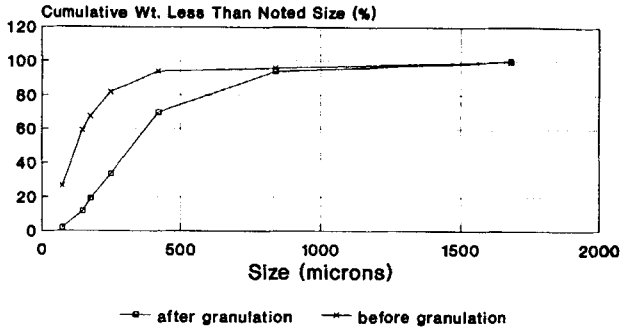

Figure 4. Cumulative frequency plot of particle size before and after granulation. 15% glycerylpalmitostearate and 15% polyethylene glycol 8000 lactose–hydroxypropyl methylcellulose formula.

dg_{50} values of 135, 145, 250, and 310 μm were obtained for 10%, 15%, 20%, and 30% w/w total amount of melt granulating materials, respectively. The shift towards a coarser particle size distribution with increasing amount of total molten granulating material is evident in the cumulative frequency particle size plot shown in Fig. 5. This result is similar to that typically observed for conventional, wet granulation processes, where increasing amounts of granulation liquid generally increase the granulation particle size distribution (11).

Table 3 shows the loss-on-drying results for the lactose–hydroxypropyl methylcellulose granulations. The moisture content of these hydroxypropyl methylcellulose melt granulations is very similar and less than the starting value of 0.91%.

The effects of different types of molten granulating materials on the power consumption profiles of the lactose–starch formulations are presented in Fig. 6. In this figure, the formulation containing 15% w/w glyceryl-

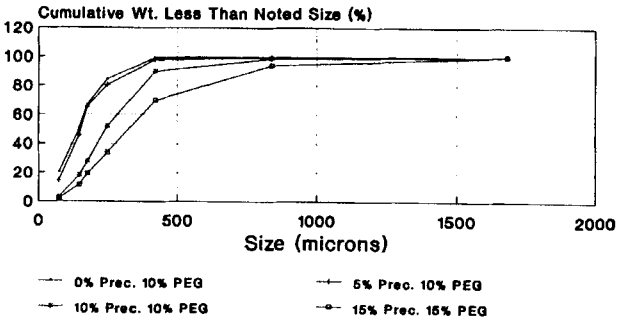

Figure 5. Effect of melt material amount on the granulation size cumulative plot. Glycerylpalmitostearate and polyethylene glycol 8000 lactose–hydroxypropyl methylcellulose formula.

Table 3

Granulation Characteristics: Lactose-Hydroxypropyl Methylcellulose Formulation

Percent glyceryl palmitostearate	0	5	10	15	15
Percent Polyethylene glycol	10	10	10	15	15
Granulation process	Melt	Melt	Melt	Melt	None
dg_{50}, μm	135	145	250	310	120
σg, μm	2.00	1.86	1.86	1.90	2.22
Percent loss-on-drying	0.78	0.65	0.65	0.65	0.91
Bulk density, g/ml	0.57	0.52	0.41	0.49	0.44
Tapped density, g/ml	0.72	0.71	0.50	0.57	0.61

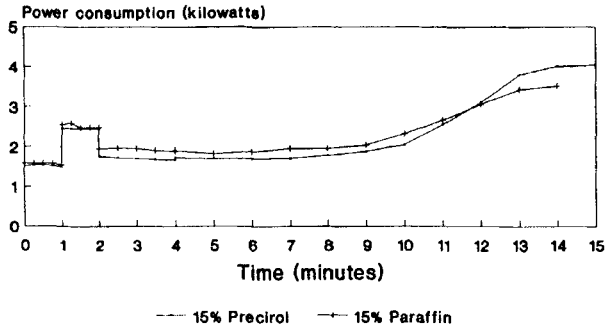

Figure 6. Power consumption for glycerylpalmitostearate and paraffin melt granulations. 15% glycerylpalmitostearate or paraffin and 15% polyethylene glycol 8000 for lactose–starch formulations.

palmitostearate and 15% w/w polyethylene glycol 8000 produced a power consumption profile very similar to that of the formulation containing 15% w/w paraffin and 15% w/w polyethylene glycol 8000. Hence the rate and extent of particle bridging obtained with these molten materials appear to be similar (11). As shown in Table 4, the formulation containing 15% w/w glycerylpalmitostearate and 15% w/w polyethylene glycol had a dg_{50} value of 380 μm versus the formulation containing 15% w/w glycerylpalmitostearate and 15% w/w paraffin, which had a dg_{50} value of 395 μm.

In Figure 7, power consumption profiles of different shape were obtained for the lactose–starch granulations containing different ratios of glycerylpalmitostearate and polyethylene glycol. The slower rate of increase in the power consumption profile for the formulation containing 30% w/w polyethylene glycol may be related to the higher melting point of polyethylene glycol versus glycerylpalmitostearate. Different average granulation sizes were also found for these formulations, as shown in Table 4.

Table 4 also indicates that the formulation containing 30% w/w polyethylene glycol 8000 has higher bulk and tapped density values than the corresponding granulation containing 30% w/w glycerylpalmitostearate. The formulation containing 15% w/w polyethylene glycol 8000 and 15% w/w glycerylpalmitostearate also has higher

Table 4

Granulation Characteristics: Effects of Increasing Amounts of Molten Materials on Starch–Lactose Formulation

Percent glyceryl palmitostearate	30	15	0	0	
Percent polyethylene glycol	0	15	30	15	
Percent paraffin	0	0	0	15	
					Wet gran: 5% Povidone, 21% Water
dg_{50}, μm	440	380	860	395	490
σg, μm	2.25	2.59	3.74	1.49	2.04
Percent loss-on-drying	2.37	1.96	2.25	2.42	3.12
Bulk density, g/ml	0.49	0.56	0.58	0.43	0.55
Tapped density, g/ml	0.59	0.66	0.68	0.56	0.66

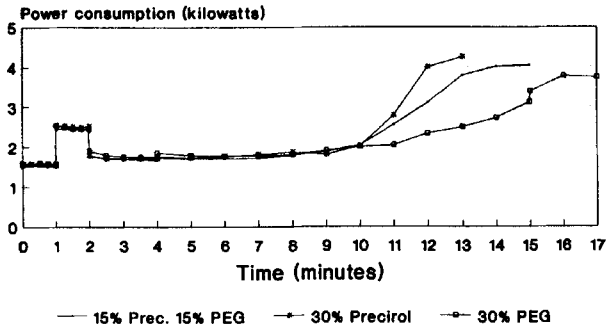

Figure 7. Power consumption for varying ratios of melt granulating materials. 0–30% glycerylpalmitostearate and/or 0–30% polyethylene glycol 8000 in lactose–starch formulations.

bulk and tapped density values than the granulation containing 30% w/w glycerylpalmitostearate. Glycerylpalmitostearate appears to produce lower density lactose–starch granulations relative to polyethylene glycol 8000.

The moisture levels for the starch–lactose melt granulations, shown in Table 4, ranged from 1.96% to 2.42%. In the melt granulation process, the moisture content of the granulation depends on the initial moisture content of the starting materials and on the time and temperature of the melt granulation heating/cooling cycle. The higher moisture values of the lactose–starch formulations versus the lactose–hydroxypropyl methylcellulose formulations are due to the higher initial moisture content of the starch (12–15%), versus that of the hydroxypropyl methylcellulose (approximately 3%).

Comparison of the disintegration times and dissolution rates from the immediate release tablets prepared by the molten and wet granulation processes are shown in Table 5. Although the wet granulation produced tablets with faster dissolution rates, acceptable dissolution rates were obtained for the tablets prepared by the melt granulation process. The tablets containing 30% w/w polyethylene glycol 8000 provided the fastest dissolution rate of the tablets manufactured by the melt granulation process. Addition of 15% w/w glycerylpalmitostearate slowed down the dissolution rate. However, further change in glycerylpalmitostearate concentration from 15% to 30% w/w did not change the release rate of the formulation.

The TAVIST sustained-release, lactose–hydroxypropyl methylcellulose formulation containing 5% w/w glycerylpalmitostearate and 10% w/w polyethylene glycol 8000 was progressively scaled up from the 75-liter Collette Gral processor to 150-liter and 300-liter Collette Gral processors. The in-process data shown in Table 6 indicate that the formulation and the melt granulation process produced comparable granulations and equivalent tablets at larger scale. The dissolution rates of these sustained-release tablets are shown in Fig. 8.

CONCLUSIONS

The melt granulation process has been found to be an efficient process that is useful for both immediate- and sustained-release dosage forms. In the melt granulation process, heating liquifies a suitable granulating material

Table 5

TAVIST Tablet Disintegration and Dissolution Data: Immediate-Release Formulations

Composition	Disintegration Time, min	Percent Dissolved at Time Points 15 min	30 min	60 min
30% Precirol; 0% PEG 8000	23	35	75	100
15% Precirol; 15% PEG 8000	18	34	69	100
0% Precirol; 30% PEG 8000	10	68	100	
5% Povidone; 21% water	<1	100		

Note. N = 6 tablets; 900 ml purified water USP; 50 rpm USP paddle method.

Table 6

TAVIST Tablet Scale-Up Data

Granulation in-process data	Laboratory Scale 9 kg; 50,000 tablets	Pilot Scale 45 kg; 250,000 tablets	Production Scale 90 kg; 500,000 tablets
Bulk density, g/ml	0.50	0.57	0.60
Tapped density, g/ml	0.63	0.78	0.77
Loss-on-drying, %	0.96	0.75	1.21
Tablet in-process data			
Weight variation average, mg (RSD%)	NA	181.2 (1.11)	179.8 (1.68)
Hardness, N	59	45	50
Friability, %	0.08	0.07	0.12

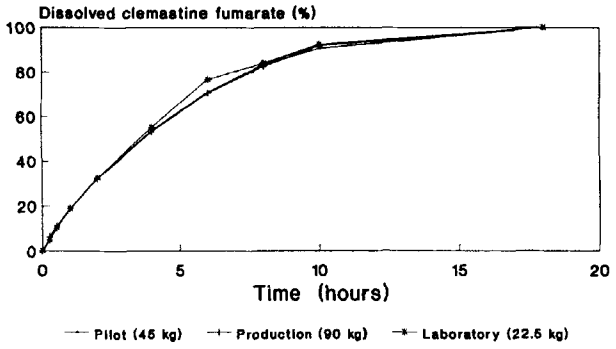

Figure 8. Effect of Scale-up on the Dissolution of Modified Release TAVIST Tablets. $N = 12$ Tablets, 900 ml purified water USP, 50 rpm USP paddle method.

that agglomerates the particles in a manner similar to the liquid addition in conventional wet granulation. Drying to remove the water in wet granulation is replaced by cooling in the melt granulation process. Both heating and cooling can be carried out continuously in the same equipment for the molten granulation process. The process can be further automated by using power consumption to detect the granulation end point. Successful scale-up of the melt granulation process has been shown through the obtainment of reproducible product characteristics at the production manufacturing scale.

REFERENCES

1. A. Royce and J. Suryawanshi, 1992 AAPS Eastern Regional Meeting, Poster No. 48, Alternative granulation techniques: Wax granulation, 1992.
2. J. Suryawanshi, R. Sandry, A. Royce, and U. Shah, 1994 AAPS Eastern Regional Meeting, Poster No. 117, Process characterization of a wax granulation technique in a high shear mixer, 1994.
3. B. Lippold, in *Oral Controlled Release Products, Therapeutic and Biopharmaceutic Assessment* (U. Gundert-Remy and H. Möller, eds.), Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1990, p. 39.
4. R. Gordon and D. Fonner, in *Pharmaceutical Dosage Forms: Tablets*, Vol. 2 (H. Lieberman, L. Lachman, and J. Schwartz, eds.), Marcel Dekker, New York, 1989, p. 245.
5. H. P. Bier, H. Leuenberger, and H. Sucker, Die Pharmazeutische Industrie, 41(4), 375–380 (1979).
6. T. Schaefer, P. Holm, and H. G. Kristensen, Drug Dev. Ind. Pharm., 16, 1249 (1990).
7. H. Leuenberger and G. Imanidis, Pharm. Tech., 10(3), 56 (1986).
8. T. Schaefer, P. Holm, and H. G. Kristensen, Acta Pharm. Nord., 4(4), 245 (1992).
9. P. Flanders, G. A. Dyer, and D. Jordan, Drug Dev. Ind. Pharm., 13(6), 1001 (1987).
10. C. M. McTaggart, J. A. Ganley, A. Sickmueller, and S. E. Walker, Int. J. Pharm., 19, 139 (1984).
11. H. G. Kristensen and T. Schaefer, Drug Dev. Ind. Pharm., 13(4&5), 803 (1987).