Effects of the Bag-Shaking Cycle on the Particle Size Distribution of Granulations

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This article discusses the effects of the bag-shaking cycle on granulations in a fluid-bed granulation process. The particle size distribution of a finished granulation can be improved if the shake time and the corresponding interval between bag shakes are optimized. — Originally appeared in *Pharm. Technol.* 13 (9), 78–82 (1989).

Fluid-bed granulators recently have become widely accepted by the pharmaceutical industry. Various technical refinements and advancements have broadened their potential applications in the wet granulating operation, and process conversion now is increasingly common. The quantity of published reports in the fluid-bed area also has increased steadily.

When fluid-bed granulators were initially developed, the filter bag was viewed simply as a device for preventing small particles from escaping the granulator. As improved shake mechanisms and filter materials became available, semiautomatic bag-shaking timers also gained wide acceptance. Another improvement, split bags, allows one portion of the bag to be cleared while the other portion remains in use.

The effects of the bag-shaking cycle on the finished granulation have not been reviewed since the advent of these new technologies. The majority of published material has addressed technical issues such as spray rates,[1] air volumes,[1,2] nozzle height,[2] process temperatures,[3] binder type and concentration,[4] equipment selection,[5] and type of granulating performed.[6-8] Little interest, however, has apparently been displayed in the equally critical operation of shaking the filter bag.

Experimental

Materials. Excipients used were microcrystalline cellulose NF, povidone USP, lactose USP, cornstarch NF, mannitol NF, and magnesium stearate NF. Three 15-kg test formulations were used in this study. Granulation 1A contained 68% starch, 28% lactose, 2% povidone, and 1% magnesium stearate. Granulation 1B contained 68% mannitol, 28% starch, 2% povidone, and 1% magnesium stearate. Granulation 1C contained 34.0% starch, 34.0% mannitol, 28% lactose, 2% povidone, and 1% magnesium stearate. All formulations contained 1% ascorbic acid.

The formulations were granulated in a fluid-bed granulator (Model 2, Aeromatic, Towaco, New Jersey, USA). Povidone was dissolved in water, and the powders were granulated using a fixed spray rate of 300 mL/min, atomizing air (3 bar), inlet air set points of 50° (mix and spray cycles) and 90° (drying cycle), and damper settings required to achieve an even powder fluidization throughout the run.

Three trial batches of each test formulation were processed. During the spray cycle, the test formulations were granulated using bag-shaking/interval combinations of 10/10, 10/30, and 10/120 s. For example, a combination of 10/120 s refers to a bag-shake duration of 10 s at intervals of 120 s. A 10-s duration for the bag shake was selected following a visual determination of the average time it took to clear the bag of particles. Intervals were established at 10, 30, and 120 s to reflect minimum, mean, and maximum values normally used in granulating. All nine trial batches were dried using identical shaking/interval cycles of 10/120 s.

Dried granulations were passed through a mill (Stokes Tornado, Stokes-Merrill, Warminster, Pennsylvania, USA) equipped with a 0.109-in. screen at medium speed. All granulations were blended with magnesium stearate for two min in a low-shear "V" blender (Patterson-Kelley Co., East Stroudsburg, Pennsylvania, USA).

Tablets were compressed using a rotary tablet press (Manesty Press Model B3B, Thomas Engineering, Hoffman Estates, Illinois, USA) to a targeted crushing strength (10 kP). In some cases, the target was not reached. The tablet size was 7/16 in. standard round concave.

Test methods. The moisture content of the granulations was determined with a moisture balance (Computrac Max Model 50, Quintel Corp., Tempe, Arizona, USA). The granulations were exposed to a 125W IR lamp for 15 min at a 90-V setting, and the percent weight loss on drying was read directly from the instrument. A mean for each granulation was calculated from samples taken at the top, middle, and bottom of the vessel.

The initial tablet crushing strength was determined immediately after compression using a hardness tester (Schleuniger Model 4M, Vector Corporation, Cedar Rapids, Iowa, USA). For each deter-

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Table I: Effect of different bag-shake cycles on the bulk density of the test granulations.

	Batch Number								
	1A			1B			1C		
Major Component	Starch			Mannitol			Starch/Mannitol		
Shake/Interval (s)	(10/10)	(10/30)	(10/120)	(10/10)	(10/30)	(10/120)	(10/10)	(10/30)	(10/120)
Bulk density (g/mL, poured)	0.70	0.72	0.74	0.54	0.55	0.60	0.64	0.63	0.65
Bulk density (g/mL, tapped)	0.75	0.75	0.78	0.60	0.61	0.66	0.65	0.67	0.70
Poured ÷ Tapped (Carr's Index)	0.95	0.96	0.95	0.90	0.90	0.91	0.98	0.94	0.93

Table II: Effect of different bag-shake cycles on the particle size distributions of the test granulations.

	Batch Number								
	1A			1B			1C		
Major Component	Starch			Mannitol			Starch/Mannitol		
Shake/Interval (s)	(10/10)	(10/30)	(10/120)	(10/10)	(10/30)	(10/120)	(10/10)	(10/30)	(10/120)
Sieve analysis (% retained)									
40	61.3	53.2	36.5	35.7	13.2	24.6	48.5	31.0	30.6
60	6.2	7.3	1.1	31.4	45.9	30.3	18.8	20.6	14.7
80	3.9	4.4	0.9	6.4	14.0	3.2	5.2	10.1	3.1
100	3.8	4.4	1.6	5.7	15.6	1.4	3.1	10.3	1.5
200	8.0	5.8	10.7	6.1	8.2	7.3	7.1	8.0	9.1
Pan	16.8	24.5	48.8	13.7	2.0	32.1	15.8	18.2	39.1
Loss	0.0	0.4	0.4	1.0	1.1	1.1	1.5	1.8	1.9

mination, 10 tablets were tested and the mean calculated. Tablet thickness was measured with a thickness gauge (Model 7300, Mitutoyo Manufacturing, Tokyo, Japan). Values reported are the mean of 10 measurements. Tablets were weighed using an automatic weighing system (Mettler Automatic Weighing System, Mettler Instrument Corporation, Hightstown, New Jersey, USA) consisting of an Epson HX-20 computer, a Mettler PM-200 scale, and a Mettler LV10 feeder. Values reported are the mean for 10 tablets.

To determine friability, at least 20 tablets were cleaned using a soft camel's hair brush and placed in a friabilator (Model 10803, VanKel Industries, Edison, New Jersey, USA). After accurate weighing, the tablets were placed in the unit's drum, which was rotated for four min at 25 rpm. The tablets were removed, brushed, and reweighed, and the loss of weight was calculated. Duplicate tests were run, and the mean percent friability was calculated.

To determine bulk density (poured), 50 g of material was weighed and poured into a graduated cylinder. The density was calculated by dividing the recorded weight by the observed volume. To determine bulk density (tapped), 50 g of material was weighed and placed in a graduated cylinder on a tap density tester (Model 10705, VanKel Industries, Edison, New Jersey, USA). The material was tapped 100 times. The density was calculated by dividing the recorded weight by the observed volume. The poured density was divided by the tapped density, and the result was reported as an absolute number (Carr's index).

Sieve analysis. One hundred g of material was placed in the top screen of a portable sieve shaker (Ro-TAP Model B, Combustion Engineering, Mentor, Ohio, USA). Granulations were shaken for 10 min using 20-, 40-, 60-, 80-, 100-, and 200-mesh screens. Sieve fractions were weighed and recorded.

Ascorbic acid analysis. Ten tablets from each lot were analyzed using a high performance liquid chromatograph to determine their ascorbic acid content. Mean values and standard deviation were then calculated.

Results and Discussion

The bulk density of each granulation, whether poured or tapped, was not significantly affected by the bag-shake cycle. Indeed, the results listed in Table I strongly suggest that this attribute may be completely independent of the bag-shake cycle.

Particle size distributions of finished test granulations reflect a general shift consistent with visual observation. As shown in Table II, test formulations with different excipient concentrations produced similar shifts in particle distributions when subjected to significantly different shake cycles. The central tendency, independent of excipient type, was for powder to form in direct proportion to the length of the shake interval. Conversely, coarse granule formation increased as the shake interval decreased.

The shake cycle also influenced granulation performance during tablet compression. Table III compares compressed tablets using the trial granulations. Again, optimum results were obtained in each case using an intermediate (30 s) shake interval. Excessively long (120 s) or short (10 s) intervals produced inferior tablets. Tablet hardness, weight variation, and friability all deteriorated in the presence of an excess of coarse or fine granules.

The mechanism by which the shake interval contributes to optimum granule formation has yet to be understood fully. Schaeffer and Worts[3,4] have classified granule type without fully accounting for the possible routes of formation. Two apparent routes were discovered from visual observations. First, loose powder falls from the bag onto newly sprayed material, forming larger granules. Second, shaken powder is immediately influenced by the spray nozzle and forms new granules as the next spray cycle begins. When repeated at a faster, more predictable rate, both mechanisms can account for a favorable shift in the particle size distribution of the granulations.

Table III: Effect of different bag-shake cycles on compressed tablets.

Major Component	Batch Number 1A Starch			1B Mannitol			1C Starch/Mannitol		
Shake/Interval (s)	(10/10)	(10/30)	(10/120)	(10/10)	(10/30)	(10/120)	(10/10)	(10/30)	(10/120)
Thickness (in.)*	0.156	0.165	0.170	0.160	0.165	0.168	0.150	0.151	0.156
Hardness (SCU)*	9.4	10.2	8.0	8.3	12.0	10.1	7.6	10.4	9.3
Weight (mg)	381	385	383	381	386	383	382	384	381
SD (mg)*	8.3	2.0	6.1	4.3	1.4	9.1	3.2	2.1	7.1
Friability (%)	0.6	0.2	1.2	0.5	0.2	0.9	0.5	0.1	1.3
Content uniformity (%)	98.0	99.2	97.6	96.4	98.3	96.4	98.1	98.4	96.4
SD (%)	4.0	0.6	9.7	6.1	1.2	10.9	4.3	1.8	9.2

*Mean for 10 tablets.

Conclusion

This article demonstrates that the bag-shake/interval cycle is an important factor to consider when optimizing a process in a fluid-bed granulator. By optimizing the shake time and the corresponding interval between bag shakes, it is possible to improve particle size distribution of finished granulations.

References

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