Evaluation of a Process Relevant Method for Determining the Robustness of Sugar Spheres as a Drug Layering Substrate

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Scott Vass, Charles Cunningham and Ali Rajabi-Siahboomi
Colorcon, Inc., Harleysville, PA USA

Purpose

The mechanical strength, particle size and sphericity of starting sugar spheres for drug layering and subsequent functional coating applications are critical to achieving a reproducible and high yield final product.[1] During early processing, spheres can be subjected to high mechanical stress that may result in the generation of fines, changes in particle size and loss of sphericity.

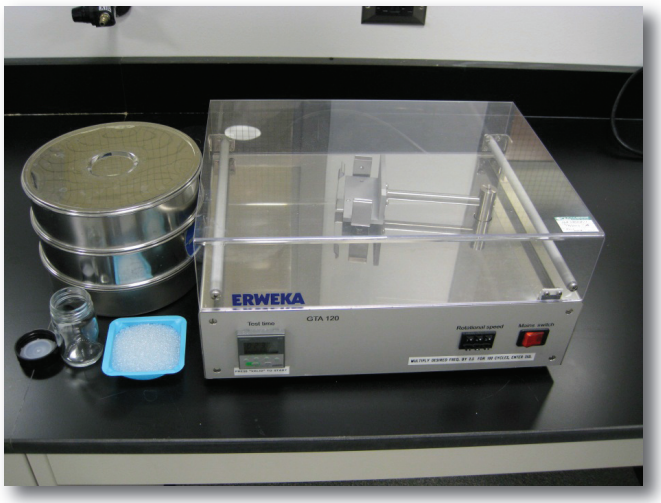
The European Pharmacopoeia describes both a fluidization apparatus and an oscillating apparatus method for determining the friability of granules and spheroids.[2] The oscillating method was shown by Christiansen et. al. to be more suitable for consistently determining the friability of pellets over a wide range of hardness.[3] These friability methods however may not be fully indicative of mechanical stresses in a production environment.

The objective of this study was to evaluate the mechanical robustness of SUGLETS® sugar spheres using the oscillating friability method as compared to attrition values generated in laboratory and production scale fluid bed processes.

Methods

Sugar spheres of 20/25 mesh (710-850µm, Suglets® PF010, Colorcon Inc., USA) were used as the substrate. Laboratory friability testing of the sugar spheres was performed using a modified methodology based on Eur. Ph. 2.9.41, Method B. The equipment used is shown in Figure 1.

Figure 1. Oscillating Friability Apparatus (Erweka GTA 120, Milford, CT, USA)



In this method, 10 g of spheres were weighed into the glass container along with 25 g of glass beads (2 mm). The container was subjected to oscillation (300/min) for 4 minutes. The sample vial was removed and emptied onto a set of sieves. The sieves included an 18-mesh sieve (1000 µm) to remove the glass beads, a 25-mesh sieve (710 µm) at the lower limit of the sphere size specification, and a pan to collect any fines. The sample was sieved for 1 minute on a Ro-Tap sieve shaker (W.S. Tyler, Mentor, Ohio, USA). The weight of fines retained in the pan was compared to the starting sphere sample weight to determine percent friability using the calculation below.

Friability Calculation

$$Friability\ (\%) = \left(\frac{Wt_f\,(g)}{Wt_i\,(g)}\right) x100$$

$Wt_f = Total\ weight\ of\ fines$, (sum of differences between start /end weights of the glass container with lid, sieve pan, and glass beads)

$Wt_i = Initial\ sample\ weight$

In another study, the sugar shperes were processed in fluid bed (Wurster configuration) coating machines (Freund-Vector Corp, USA) for varying times and atomization pressures, at both laboratory (2 kg) and production scale (50 kg). The process schematic is shown in Figure 2 and the trial parameters are shown in Table 1.

Table 1. Fluidization Process Conditions (1 and 4 Bar Atomization Pressures)

Parameters	Laboratory Scale		Production Scale	
	VFC 3	VFC 3	VFC 60M	VFC 60M
Column (cm, in)	17.8, 7.0	17.8, 7.0	45.7, 18.0	45.7, 18.0
Partition Gap (cm, in)	1.0, 2.5	1.0, 2.5	1.0, 2.5	1.0, 2.5
Bed Temperature (ºC, ºF)	30, 86	30, 86	30, 86	30, 86
Atomization (bar, psi)	1.0, 14.5	4.0, 58.0	1.0, 14.5	4.0, 58.0
Air Volume (m^3 /hr, CFM)	170, 100	170, 100	1359, 800	1359, 800
Charge (kg)	2.0	2.0	50.0	50.0
Duration (min)	10 and 30	10 and 30	10 and 30	10 and 30

After fluidization, the process friability was calculated by determining the batch weight of sugar shperes that remained on a 710 µm (25-mesh) sieve using the calculation below.

Process Loss / Friability Calculation

$$Loss\ (\%) = \left(\frac{Wt_i(g) - Wt_f(g)}{Wt_i(g)}\right) x100$$

$$Wt_f = Total\ sample\ weight\ after\ screening$$

$$Wt_i = Initial\ sample\ weight$$

Samples (30 g) were also removed during the fluidization process at 5, 10, and 30 minutes and evaluated for sphericity and particle size distribution by dynamic image analysis (Camsizer, Horiba, Edison, NJ, USA).

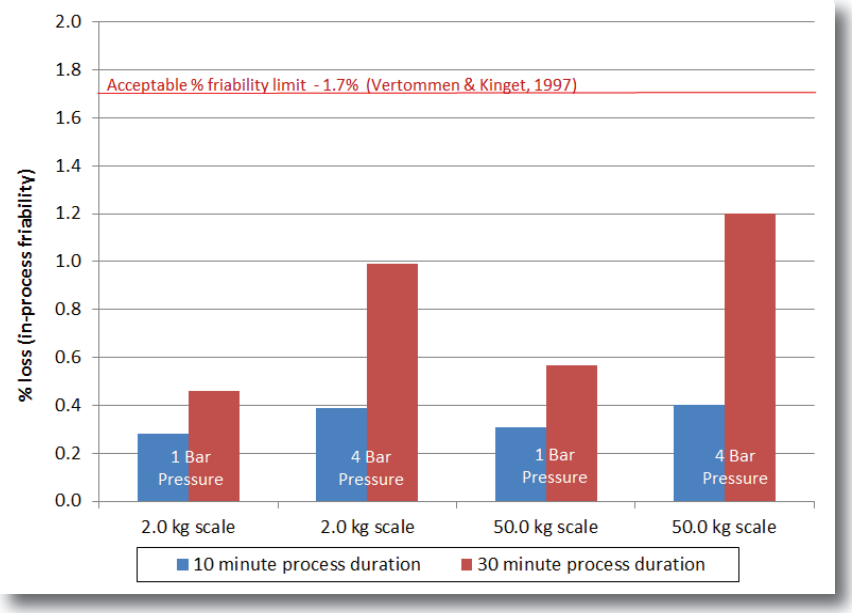
Results and Discussion

Pharmacopeial methods do not specify acceptable friability limits for sugar spheres, however friability values of <1.7% w/w friability have been reported as acceptable to withstand stresses associated with fluid bed coating, handling and other processes.[4] The friability for sugar spheres using the oscillating test method was 0.6% w/w, well below this reported limit.

Exposure of the sugar spheres to fluidization (without spray) in the fluid bed process for 10 minutes was representative of the typical pre-heating time and stress to which spheres are exposed prior to the application of coating. Generally, a small amount (0.5 – 1.0 bar) of atomization air is also used during this stage to prevent nozzle blockages. At both, laboratory or production scale, friability of the sugar spheres was <0.4%.

Friability of sugar spheres after an extended 30 minutes of fluidization (50 kg scale) was < 0.6% at 1 bar of atomizing pressure (commonly used setting) and <1.2% at 4 bar of atomizing pressure despite increased particle velocity and impingement forces. The results of the fluidization trials are summarized in Figure 5.

Figure 3. Friability Values for Process Fluidization Trials



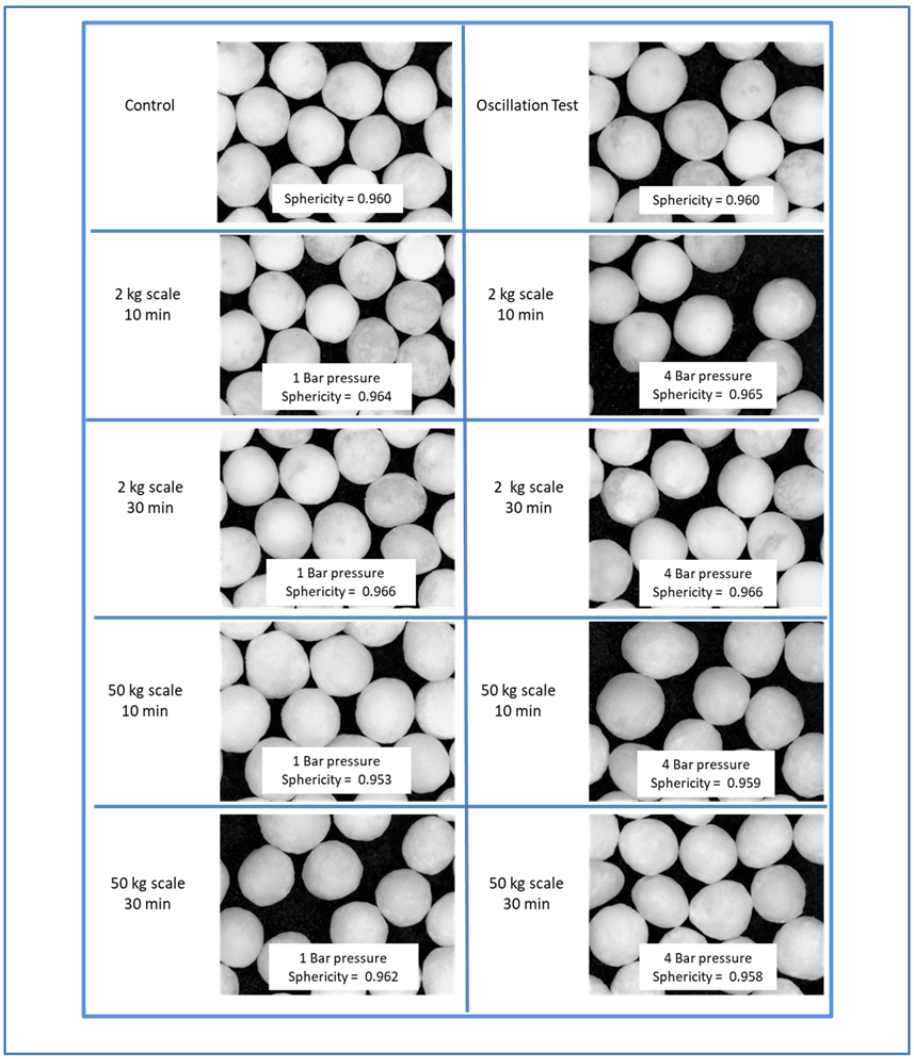
For all samples, particle size distribution remained consistent (Table 2).

Table 2. Particle Size of SUGLETS after Exposure to Friability Tests

Test Method	Atomizing Pressure (bar)	Exposure Time (min)	Particle Size (µm)		
			d (0.1)	d (0.5)	d (0.9)
Control	-	0	721	796	866
Oscillator	-	4	726	788	849
Laboratory scale fluid-bed (2kg charge)	1	10	725	788	850
		30	726	789	851
	4	10	725	788	850
		30	723	787	849
Production scale fluid-bed (50kg charge)	1	10	736	811	887
		30	736	811	885
	4	10	737	812	887
		30	732	808	883

After processing, there were no signs of fracture or broken particles, visually or under magnification. The sphericity of the sugar spheres was also unaffected by processing with near perfect roundness maintained for all samples having values ≥0.953 (see Figure 4).

Figure 4. Appearance and Sphericity of SUGLETS after Processing



Conclusions

The results indicated that the current laboratory methods used for evaluating the friability, particle size and sphericity of sugar spheres are appropriate for ensuring the robustness of SUGLETS sugar spheres in fluid bed processes. Only under the most extreme fluid bed conditions (4 bar atomizing pressure) did friability values exceed those obtained in the laboratory friability apparatus. In this study, SUGLETS exhibited ideal characteristics for drug layering / loading and functional coating applications.

References

1. Werner D., Sugar Spheres: A versatile excipient for oral pellet medications with modified release kinetics. *Pharmaceutical Technology Europe*, 2006, Vol. 18 Issue 4, p35.
2. European Pharmacopoeia 8.0, 2.9.41 Friability of granules and spheroids, p359-361.
3. Christiansen C. and Müller B., Friability of granules – Evaluation of different test methods, *Pharm. Ind.*, 2002, Vol. 64, Nr. 4, p390-397.
4. Vertommen, J. and Kinget, R., The influence of five selected processing and formulation variables on the particle size, particle size distribution, and friability of pellets produced in a rotary processor, *Drug Dev. Ind. Pharm*., 1997, Vol. 23, p39-46.