

## Technical Evaluation of SureSpheres™

### 20/25 Mesh (850-710 micron) as starter seeds

#### APPLICATIONS DATA SUMMARY

- Physical properties and batch-to-batch consistency of nine batches of 20/25 mesh beads have been analyzed.
- Friability, hardness, particle size, sphericity, density, surface roughness....
- Demonstrated that SureSpheres 20/25 mesh are high quality, consistent substrates for pharmaceutical drug layering and coating applications.

#### INTRODUCTION

SureSpheres, drug layering substrate, are defined as small, free flowing, spherical pellets manufactured by the agglomeration of fine powders. There has been a continued interest for the use of pellets in multiparticulate drug delivery systems over single–unit dosage forms due to their clinical and formulation advantages, and ease of processing in immediate and modified release applications.

Pellets provide formulation flexibility by allowing precise control of drug dose, separating incompatible active pharmaceutical ingredients (API), and reducing clinical variability (1). Drug release from multiparticulate pellets is controlled by the application of a polymeric film coating onto the drug loaded pellets. Drug loading onto the surface of pellets is accomplished via dry powder layering or by spraying an aqueous/organic solution or dispersion of the drug.

Selection of pellets as starter seeds with consistent quality is critical to the performance of the multiparticulate formulation, as these are the foundation for which drug and coating layers will be applied. Factors that have been identified as critical to successful drug loading and modified release from multiparticulates are surface roughness and sphericity, particle size and its distribution, density, friability and hardness of the starting substrate (2, 3).

Pellet surface roughness, sphericity, and particle size distribution influence the quality and reproducibility of a drug layer, while pellet density impacts the flow, and fluidization during coating processes as well as filling of multiparticulates into capsules. Low friability and high hardness of the starting pellets are required to withstand the rigors of the drug layering process, subsequent coating, and packaging steps. A narrow and consistent particle size distribution allows for the application of a consistent quantity of API and functional

coating per pellet in a batch. In addition, it ensures reproducible performance and batch-to-batch consistency. Multiparticulate size distribution can also influence the degree of segregation during blending or filling (3).

The objectives of this study were to characterize the physical and mechanical characteristics of 20/25 US standard mesh (850-710 micron) sugar spheres (SureSpheres™) and to evaluate their batch-to-batch consistency.

## MATERIALS AND METHODS

Nine lots of SureSpheres (20/25 US Standard mesh, NF26) (Colorcon, USA) were tested as follows:

### Particle Size Analysis

The particle size distribution of SureSpheres samples was determined by sieve analysis using a RoTap sieve shaker (Model RX-29, W.S. Tyler, USA). Two hundred grams ( $\pm 2.5$  g) of pellets was sieved through four different sizes of mesh screen (18, 20, 25, 30 mesh) and the fines were collected in the pan.

Specification limit NF 26 for pellets of 20/25 mesh, states that the entire sample pass through an 18 mesh sieve, not less than 90% of the starting sample should pass through a 20 mesh sieve, and not more than 10% passes through a 25 mesh sieve (4).

### Loss on Drying (LOD)

Approximately 1.5g of SureSpheres was used in the loss on drying method described in the NF 26. Pre-weighed samples of SureSpheres were dried in a temperature controlled oven at 105°C for 4 hours. The weight of the samples before and after the drying was used to calculate the loss on drying of the samples. The specification limit of the test was established in the NF 26 as not more than 4.0% of its weight.

### Bulk Density

The bulk density was determined by measuring the volume of 50 g of SureSpheres into a 100 mL graduated cylinder. Density was calculated by the formula below and expressed in g/mL:

$$(M) / (V_0)$$

M: Mass of test sample

V<sub>0</sub>: Apparent volume of test sample

as described in the NF 26. Duplicate determinations were recorded and the mean value was calculated.

### **Determination of Hardness**

The breaking force required to break a single sphere was used to describe the hardness of SureSpheres. The hardness of 20 single spheres collected from the 20, 25, and 30 mesh size screens retains, were tested using a Texture Analyzer (Model TA.XT.Plus, Texture Technologies Corp., USA). The hardness of each pellet was measured using a ½ inch diameter, cylindrical probe (TA-10), 5 kg load cell, 0.1mm/sec probe speed, 70% strain and a trigger of 5 g (Auto mode).

### **Friability/Abrasion Test**

Currently there is no standard test method established for evaluating friability of pellets. However, friable pellets are not desirable as starter seeds for drug layering and a measure of extent of friability of pellets is important. Here, a modified USP friability tester, called the “abrasion drum” (Vankel Industries Inc., USA, Figure 1), was used. The friability test was made feasible for SureSpheres despite their small particle size (compared to tablets) and light weight.

*Figure 1 – Vankel Abrasion Drum*



The drum used in the USP friability test for tablets has a single curved baffle, which allows the tablets to rise and then drop from a distance of approximately 156 mm height. When testing SureSpheres, the standard friabilator drum causes the samples to roll and fall during the test, while the abrasion drum can generate two different types of motion depending on how the abrasion drum is mounted to the friabilator arm. One motion generates a cascading movement of the spheres from one lamella to the other, while the other motion raises the spheres up and drops the spheres from a distance of approximately 200 mm. In this study the abrasion drum was configured to raise and drop the SureSpheres samples from 200 mm. The method was further modified by adding 1 mm glass beads to the pellets, increasing the stress level on pellets, similar to conditions in fluid bed coaters.

A sample of approximately 10 g of SureSpheres and 25 g of glass beads (1 mm size) were added to the abrasion drum and tested for 10 minutes at 25 rpm. The friability results were reported as the percentage of the spheres that passed through the 25 mesh sieve size, after the test.

## Roundness/Aspect Ratio

Characterization of the sphericity or roundness of SureSpheres was conducted by Particle Technology Labs (Downers Grove, IL, USA). Automated microscopy and image analysis techniques (PharmaVision 830, Malvern Instruments Inc., USA) were used to characterize the morphology of SureSpheres, and to calculate mean roundness and aspect ratio. Aspect ratio is defined as the ratio of the length of a pellet divided by the width, with pellets being considered round (spherical) if the aspect ratio lies between 1.00 and 1.20 (5).

Roundness is a measurement of the length/width relationship, with values in the range 0 – 1. A perfect circle has roundness 1.0, while a needle shaped object has roundness close to 0. The roundness is typically determined using the equation:

$$\text{Roundness} = (4 * \pi * A) / P^2$$

Where A is the measured area and P is the perimeter of the pellets.

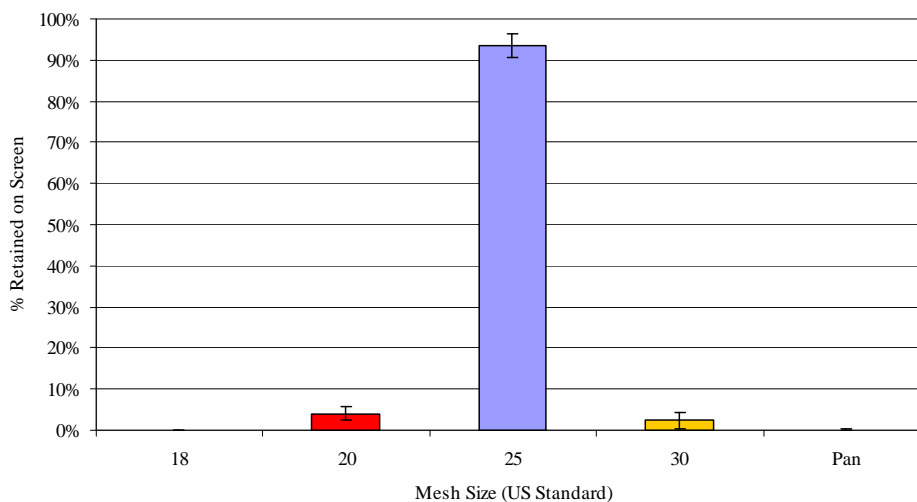
## Surface Roughness

The surface roughness characterization of the SureSpheres was measured (Micro Photonics Inc, Irvine, CA, USA), using the axial chromatism technique and profilometry measurements of the sphere surface (Nanovea ST400, Micro Photonics Inc., USA). Amongst different roughness values reported, the Sa values (arithmetical mean height or mean surface roughness) were used as main reference in the comparison of surface roughness of SureSphere samples. A high Sa value indicates a high degree of surface roughness for the spheres.

## RESULTS AND DISCUSSION

### Particle Size Analysis

**Figure 2 – Particle Size Distribution of SureSpheres 20/25 Mesh**  
(Error bars denote standard deviations for 9 samples)



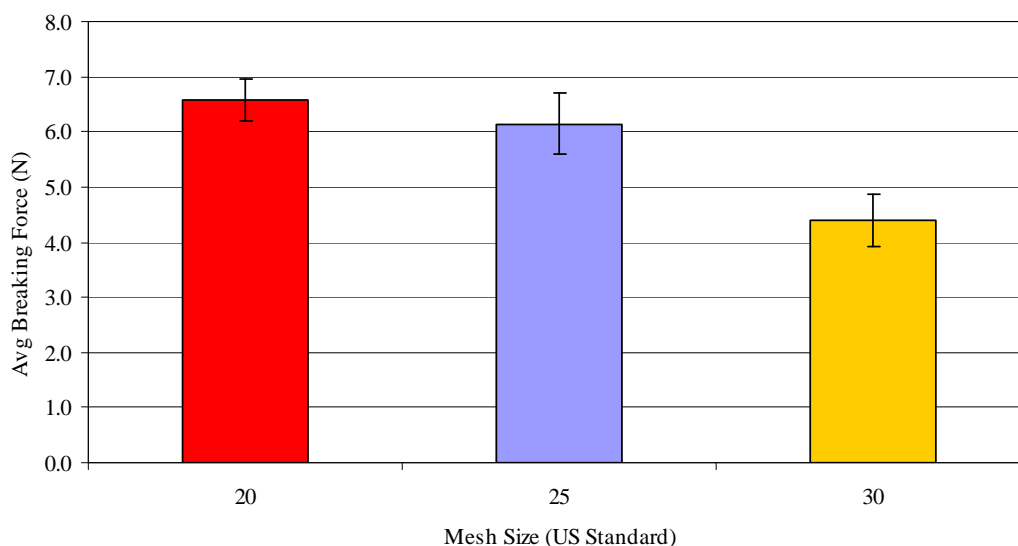
The particle size distributions of all samples were comparable and in compliance with the NF 26 specifications.

### Breaking Force

Figure 3 summarizes mean hardness values of the 9 lots for 20 pellets per lot collected on the 20, 25 and 30 mesh screens. Results indicate that 20/25 mesh SureSpheres have similar hardness values amongst different batches, at each mesh size, ensuring uniform mechanical strength for drug layering and coating operations.

**Figure 3 – Breaking Force**

(Error bars denote standard deviation for **9 lots**, 20 pellets per mesh, per lot)



### Loss on Drying, Friability, Surface/Pellet Morphology, and Density

**Table 1 – Physical Properties of SureSpheres**

	Mean	Standard Deviation (SD)
Loss on Drying (% , n = 3)	2.5	0.8
Friability (%)	0.7	0.4
Surface Roughness (Sa Value)	2.93	0.56
Roundness	0.86	0.03
Aspect Ratio	1.16	0.06
Bulk Density (g/mL)	0.83	0.02

Loss on drying results shows that each of the 9 lots met the USP requirements of not more than 4.0% (4) with a mean of 2.5%. Friability of the pellets even under high stress was low with a mean value of 0.7%. Interpretation of the pellet hardness and friability results indicates minimal lot-to-lot variation, and a strong robust substrate for drug layering and coating processes.

The mean aspect ratio for the 9 lots was less than 1.2 with roundness values at 0.86, indicating that the pellets are spherical, and thus suitable for capsule filling and coating processes (6). The mean surface roughness for 9 lots of SureSpheres highlight that a similar, smooth surface is observed across different batches.

Bulk density values of 0.83 and a small standard deviation provide a very low degree of variation from batch to batch, which allows uniform fluidization during coating, filling at commercial scale, and minimizes segregation during any blending operations (2).

## **CONCLUSIONS**

Nine lots of SureSpheres 20/25 mesh (850-710 micron) were analyzed for parameters that are considered as critical to a quality substrate for drug layering and coating processes.

Results showed that SureSpheres had minimal variation in any of the parameters examined. Uniform high hardness and low friability were observed, which ensures consistent mechanical strength and robustness for coating processes. Particle size, shape, and surface characteristics indicate a uniform, spherical surface for optimal deposition of drug and coating layers.

SureSpheres possess physical properties that are ideal for a starting substrate, for pharmaceutical drug layering and subsequent coating and compression operations.

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