Optimization of Extrusion Spheronization Process for Multiparticulates via Design of Experiments

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Purpose

This study evaluates the extrusion-spheronization process for preparing drug loaded multiparticulates. Formulation and several processing parameters were evaluated through design of experiments (DOE). The goal was to understand the impact on particle size and distribution, sphericity, friability and yield of the target bead size as compared to a standard sugar sphere product.

Methods

Four factors: binder level, water level, spheronization speed and, spheronization time, were studied in a Model Robust response surface design with 27 runs using DOE Fusion Pro. Metoprolol, commonly presented as a multiparticulate product, was chosen as the model drug for this study. A drug loading of 40% was selected due to the high solubility of the drug. Starch 1500®, partially pregelatinized starch, was used as the binder in the formulation and varied from 1 – 7%. The balance of the formulation was microcrystalline cellulose (50 micron). 750 g batch sizes were produced using wet granulation in a Glatt VG 25M high shear granulator with a 5 L bowl. Water was sprayed into the granulator with a pneumatic nozzle and pumped at a constant rate for all batches. The wet mass was then extruded through an LCI MG-55 extruder with a 1mm x 1mm dome die. The extrudates were spheronized with different speeds and times using an LCI QJ-400TG spheronizer fitted with a 2 mm friction plate. Resulting beads were dried in a Glatt GPCG-3 fluid bed dryer. Batches were analyzed using a Camsizer P4, dynamic image analyzer and then sieve cut with 16 and 20 US mesh screens representing the target bead size acceptable ranges. The yield of target size beads was then determined. Batches were again analyzed with the Camsizer to evaluate size and shape. Each batch was tested for friability using an Erweka GTA 120 friability tester. Select batches were evaluated with an optical microscope and tested for dissolution to determine drug release variations.

Results

All batches manufactured in this study processed well and there were no issues with any stage of the process. A wide range of bead shapes and sizes were produced through the DOE. Water level was the most significant factor impacting nearly all the responses studied. In some cases, when the water level was high, beads would agglomerate during the spheronization process and produce over-sized beads. Camsizer analysis showed that similar factors impacted the particle size, span and sphericity of the beads, before and after the sieving process. Figure 1 shows the range of D(0.1) to D(0.9) for each run prior to sieving, with comparison to 16/20 mesh Suglets® sugar sphere, PF019. Also marked on Figure 1 are the sizes representing the 16 and 20 mesh screens, as well as the target size of 1 mm or 18 mesh. Figure 1, shows the wide particle size ranges obtained in the DOE. Balancing the process parameters is required to achieve the target particle size in this process; high or low water levels will produce either over-size or under-size beads. By contrast, the sugar spheres analyzed for this product shows a very tight distribution. A narrow particle size distribution is required in order to minimize variation in film thickness of the subsequent controlled release coating and minimize dissolution variation. In the process of manufacturing extruded- spheronized beads, a sizing step is used to remove over and under-size beads from the product. Focusing on the sieved beads, Table 1 shows the range of responses measured for the study.

Figure 1. Range of Particle Sizes for Each Run Before Sieving

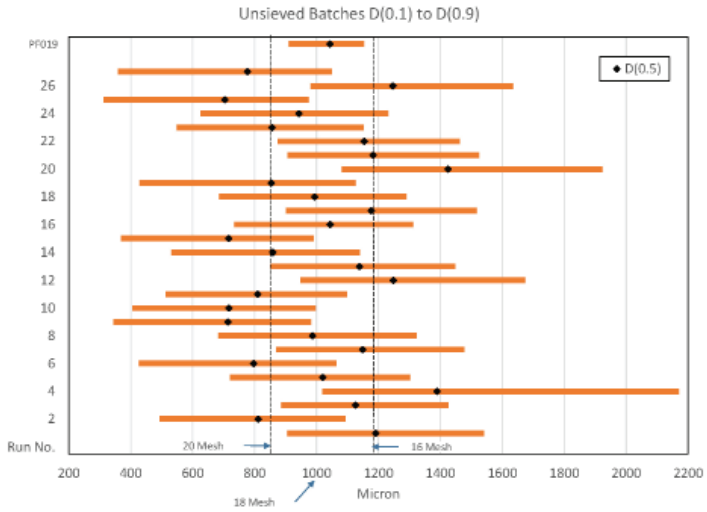


Table 1. Range of Experimental Results After Sieving

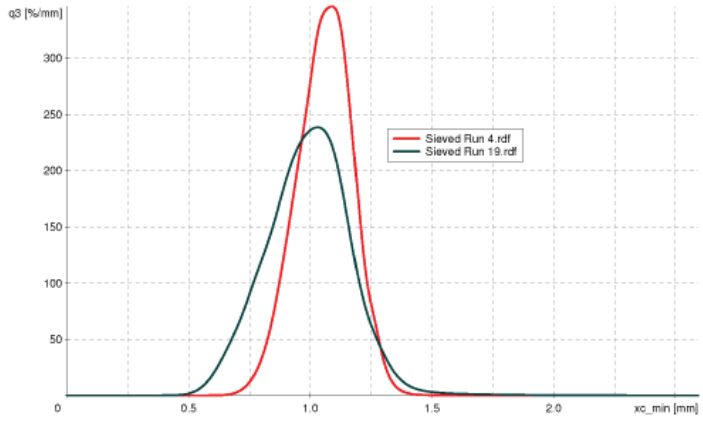
Response	Minimum	Maximum
D(0.1) (micron)	727	940
D(0.5) (micron)	919	1100
D(0.9) (micron)	1088	1246
Sphericity	0.846	0.961
Span	0.273	0.425
Friability (%)	0.10	19.08
Yield (%)	23.7	67.4

Yield of the batches, based on the target bead size, spanned a wide range and only reached a maximum of 67.4%. Depending on the parameters chosen for a given product, significant waste can be generated in this process. The lowest yield was seen when the water, spheronization speed and time were at the highest levels; whilst, the best yield was seen with all parameters at the mid levels. The high solubility of the drug and the high loading in the formulation is believed to impact this significantly as in many cases, higher yields are achievable with extrusion-spheronization. A wider range of sieve screens could also increase the acceptable yield, for instance 14-25 mesh, however, this could potentially produce higher variability in drug release after coating. Optical microscopy showed dramatic differences in the bead shapes resulting from the various runs. The highest sphericity was seen with the highest water level, spheronization speed and time, at the midpoint Starch 1500 level (Figure 2); while the lowest sphericity was seen with the lowest water level, Starch 1500 level, spheronization speed and time (Figure 3). The same trends were seen with regard to friability. Less spherical beads showed higher friability. In general, when more water was used in the process, the beads were more spherical, had a low span, and were low in friability but larger than the desired size and low in yield. These results oppose each other in terms of producing an ideal spherical shape and distribution, while attaining a high yield.

Figure 2. Highest Sphericity (Run 4)

Figure 3. Lowest Sphericity (Run 19)

Figure 4. Camsizer Particle Size Distributions



These runs also produced the tightest distribution of bead sizes and the widest distribution of sizes, reported as the span by the Camsizer respectively. Figure 4 shows these distributions. Run 19 produced a wider distribution because the bead shape impacted the sieving process. The deviation from sphericity made the sieving process more difficult, resulting in a wider distribution.

An optimization routine was run in the software to produce the targets shown in Table 2. DOE Fusion Pro will create a design space map based on the ranges to be evaluated. In Figure 5, the white area represents the space that would produce beads complying with the limits set. The colored areas show the regions where each response would start to exceed the limit set in the optimization routine. A confirmation run was produced at the optimal settings. The predicted and actual results are also shown in Table 2. Dissolution of drug from the beads were all similar, releasing all drug within 15 minutes regardless of processing and formulation variations.

Table 2. Optimization Targets and Results

Response	Objective	Limits
D(0.5) (micron)	Target	1040 - 1070
Sphericity	Maximize	0.900
Span	Minimize	0.350
Friability (%)	Minimize	2.00
Yield (%)	Maximize	52.0
Factor		**Setting**
Water Level (%)		15.0
Starch Level (%)		5.5
Spheronization Speed (rpm)		600
Spheronization Time (min)		2.0
Response	**Predicted**	**Actual**
D(0.5) (micron)	1055	1043
Sphericity	0.916	0.930
Span	0.344	0.341
Friability (%)	1.82	1.40
Yield (%)	56.3	61.3

Figure 5. Design Space

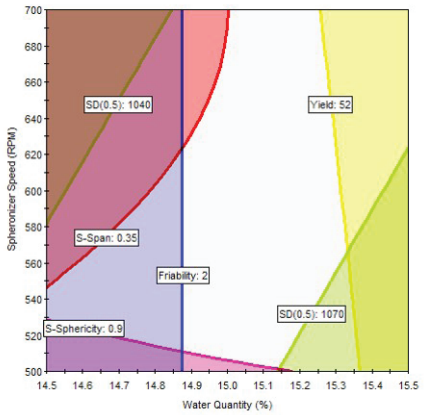
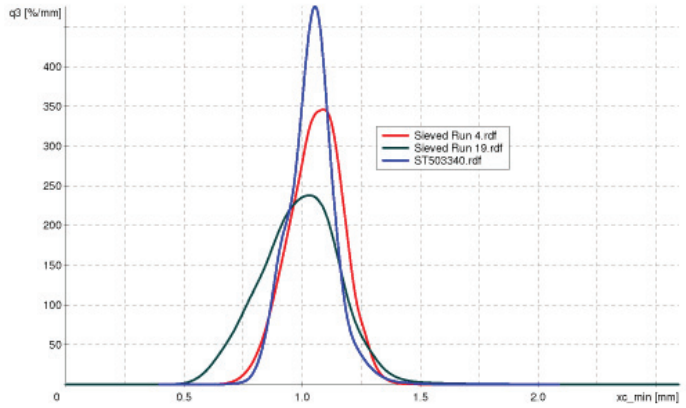


Figure 6. Camsizer Particle Size Distributions Compared to Suglets 16/20 Mesh



This data was contrasted to commercially available sugar spheres (Suglets, Colorcon) of the same size range, Table 3. Camsizer distribution of the Suglets is also compared to the previously shown distributions for runs 4 and 19, Figure 6. Run 4 nearly matches the tightness of the distribution of the sugar sphere but only produced a 24% yield of target particles. Using Suglets as a starting substrate for a drug layering process would potentially result in higher yields for the final product, as there is no sieving waste from the original product. In addition, a much tighter particle size distribution is seen with the sugar sphere, as well as lower friability and higher sphericity. These factors may have influence on the resulting dissolution of a controlled release multiparticulate product.

Table 3. Sugar Sphere Data

Response	Suglets 16/20
D(0.5) (micron)	1043
Sphericity	0.964
Span	0.232
Friability (%)	0.60
Yield (%)	100%

Conclusions

The model formulation showed high sensitivity to the water level used in the granulation phase of the process, impacting the quality of the resultant sphere properties. High sphericity and low friability can be obtained from the extrusion spheronization process; however, the parameters used to produce product in the best ranges, can result in significant waste in the process by not meeting the appropriate target size. The largest and most spherical beads, with the lowest span, was produced with the factors at the high levels; while, the smaller and the least spherical beads, with the highest span, were produced with the factors at the low levels. Beads with low sphericity produced highest friability and the largest span in particle size due to their irregular shape. Compromises in the key responses must be made to balance the key response outputs. The DOE allowed for good prediction of the responses studied as demonstrated by the confirmation run. Dissolution of the uncoated beads was not impacted by variations in the formulation or process used to manufacture them. Utilizing sugar spheres rather than the extrusion-spheronization process can result in more consistent and robust multiparticulates. The next phase of this study will evaluate drug release variation after coating the beads with a barrier membrane coating compared to a drug layered sugar sphere.

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