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1 Screening Method for Producing Suitable Spray-dried HA powder for SLS application

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9 Abstract

10 Screen methods are time-saving tools, assisting the establishment of a new process or technique
11 for laboratory and industrial scale. This paper presents a step-by-step approach to use spray drying (SD) for
12 obtaining hydroxyapatite (HA) powder, with suitable characteristics to be used as a filler in a polymer
13 matrix, for selective laser sintering (SLS) processing. The proposed method consists of adjusting the
14 departing HA suspension and SD processing parameters, briefly discussing relevant elements that must be
15 considered. Suspension's rheological behavior and spray-dried powder morphological features were
16 investigated, serving as selection criteria for the favorable set-up. Variations on slurry feed and atomization
17 pressure of SD processing parameters have allowed obtaining different powder characteristics. A major
18 influence of atomization pressure variation was identified, a greater pressure value resulted in smaller
19 particle size. Desirability function was employed to determine the optimal SD processing parameters, in
20 other words, conditions that made it possible to obtain spherical particles with the proposed mean
21 diameter in the range of 15 to 25 μm , with narrow particle size distribution.

22 **Keywords:** spray drying, hydroxyapatite, selective laser sintering, tissue engineering.

1. Introduction

Customized fabricated parts are required in a wide range of applications, being particularly important in medicine. The feasibility of manufacturing complex geometries, combining different materials, matches with the requirements of implantable devices used for human tissue recovery. Tissue engineering (TE) seeks to restore, maintain, or improve damaged tissues through the combination of scaffolds, cells, and biologically active molecules into functional tissues [1].

Human bone is a complex vascularized structure, composed of organic collagen fibrils and inorganic calcium phosphate (CaP) crystals [2]. CaP materials [3,4] such as hydroxyapatite (HA) and beta-tricalcium phosphate (β -TCP) are widely used as bone substitutes and are commercially found in a few different geometries (e.g. granules and sticks). However, the fabrication of customized scaffolds from these materials remains a challenge, especially in terms of patient's implant fitting. Additive manufacturing (AM) is a breakthrough technology that allowed significant progress for tissue engineering applications, and still reveals promising solutions for custom-made bone scaffolds [5–8].

Powder bed fusion, frequently referred to as selective laser sintering (SLS) is one of the commercially available AM processes [9]. In this process, particulate materials are fused layer by layer via heat supplied by an infrared laser source, creating 3D parts that were originally designed using computer-assisted design (CAD) tools. SLS does not need any support during manufacturing and presents high resolution and fast processing. On the other hand, SLS is carried out at high processing temperatures and the manufactured parts are characterized by a rough surface finish [10]. Nevertheless, SLS can be considered one of the most versatile AM techniques in terms of material usage and structural stability. Moreover, through optimized parameters, it is possible to achieve the desired mechanical properties for TE scaffolds [11]. SLS processing with proper materials selection can contribute to enhancing the scaffold's final properties, particularly bioactivity [12,13]. When processing composite materials (*i.e.* bioceramic fillers in a polymeric matrix) a substantial difference between material's particle size is beneficial, allowing the filler to occupy voids in the interstices of matrix particles. Concerning polymer SLS feedstock, there are preferable powder

49 characteristics that improve the sinterability and final properties of the fabricated piece [14,15]. Related
50 literature has indicated better processing and geometry accuracy when using spherical particles and
51 narrow particle size distribution with an average size below 150 μm or equivalent to the laser beam
52 diameter [14,16]. Spherical HA particles can be obtained by different techniques [17–23] in a diverse range
53 of particle sizes. However, process scalability remains a challenge and not all techniques are capable of
54 producing particles in the range of 15 to 25 μm .

55 Spray drying (SD) consists of the transformation of a fluid material into dried particles. SD had shown
56 remarkable development in the last decades, being used by different industries [24]. SD commercial
57 equipment may differ in terms of configuration. Rotary, hydraulic and pneumatic nozzle atomizers are
58 commonly used [15]. The variables that affect how the spray is mixed with the hot gas depend upon the
59 type of gas flow: co-current, countercurrent, or mixed flow [25]. Spray-dried HA (SDHA) powder has been
60 successfully employed for distinct biomedical applications, using different manufacturing techniques [26–
61 31]. Moreover, SD enables advantageous powder characteristics that are desirable for 3D printing use [24].
62 Although SDHA powder morphology indicates suitability for SLS processing, publications concerning this
63 subject are scarce [32]. Similarly, comprehensive information about how to produce SDHA powders for SLS
64 processing is rarely reported in the literature. This paper proposes a screening method for producing
65 suitable HA powders for SLS processing.

67 2. Materials and methods

68 2.1. Materials and compositions

69 Suspensions to be spray-dried were prepared with nano-sized HA [$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$] synthesized in-
70 house by hydrothermal route. Synthesis further details can be found elsewhere [33]. Methylcellulose
71 (Methocel A15 Premium LV, Dow Chemical) was added as a binder to form an aqueous suspension using
72 deionized water, according to the compositions in Table 1.

74 Table 1 – Compositions of spray-drying HA aqueous suspensions.

75
76 2.2. Spray drying parameters

77 A mini spray drying machine (Buchi B-290) was used. As displayed in Figure 1, the slurry mixture is
78 pumped through a pneumatic external mixing nozzle (2) and sprayed by the spray gas (1) into the drying
79 chamber (4). The drying gas (3) is heated and serves as a carrier for the spray-dried particles that will be
80 deposited in the recipient (5) under the cyclone (6). Larger particles that were not carried by the drying gas
81 can be recuperated under the drying chamber. Smaller particles will be retained in the filter (7).

82 Some spray drying parameters were kept constant in all experiments: inlet temperature of hot air
83 170 °C, volume flow of hot air aspiration 39 m³ h⁻¹, slurry feed 21 mL.min⁻¹ and atomization flow 45 mmHg.

84
85 Figure 1 – Scheme of BUCHI B-290 mini spray drying [34].

86
87 A pneumatic nozzle with 2.00 mm diameter was used. It is possible to rotate the nozzle cap in order
88 to get different widths of the spraying cone. Nozzle circumference of 8.5 mm was divided in 5 positions: 0,
89 I, II, III, IV, whereas position 0 was only used as a point of referent (nozzle cap tightest position). Each
90 position represents a different width of the cone spray produced by the nozzle, being position I the widest
91 cone spray.

92 The intention is to use spray dried HA particles as a filler in a polymeric matrix. In this sense, better
93 homogeneity and cohesion within materials can be achieved when HA particles are smaller and can be
94 located in the voids of polymeric particles. Therefore, to obtain spherical HA particles, possessing an
95 average diameter of 15 to 25 µm and narrow particle size distribution, two SD parameters were varied
96 slurry feed and atomization pressure. A factorial design experiment with two factors and two levels was
97 carried out (Table 3). The optimal point among the experimental results originated from factorial design

was determined using a desirability function. Results were ranked by preferable attributes taking into consideration the D50 value, (D90-D10)/D50 and particle morphology.

2.3. Characterization of powder and suspension

Morphological analysis was performed using a scanning electron microscope (SEM, JEOL IT300LV), after coating the samples with platinum (Agar Scientific). Departure HA powder was analyzed, without coating, using a field emission gun microscope (FEI, Quanta 450). Particle size and distribution (PSD) were determined by a laser scattering (Partica LA-950V2, Horiba). The specific surface area was measured by nitrogen adsorption (ASAP 2020, Micromeritics) and calculated according to the Brunauer–Emmet–Teller equation. X-ray diffraction (XRD, D8 Advance, Bruker) was carried out with a scan range from 27° to 40°, 2 θ of 0.02° and acquisition time of 5 s. For XRD phase identification, EVA software was employed using HA's diffraction pattern (Powder Diffraction Files – PDF: 00-09-0432) from International Center for Diffraction Data (ICDD). The rheological behavior of HA slurries was assessed with a concentric rheometer (AR1500 TA Instruments, US) using a 40 mm parallel plate. Rheology flow sweep measurements were performed on suspensions 20 °C, namely 10 points over stress rates from 0.1 to 40 Pa. The Herschel–Bulkley model was fitted to experimental data. After spray drying, the sprayed powder was submitted to thermal treatment using ramps of 3 °C/min up to 500 °C, for binder removal, and 10 °C/min up to 1000 °C, with a hold at this temperature for 1 h, for densification (LHT 04/17, Nabertherm GmbH).

3. Results and discussion

3.1. Raw powder characteristics

The synthesized HA powder had a specific surface area of around 80 m² g⁻¹. As a means to reduce its reactivity, the powder was heat-treated at 650 °C for 30 min resulting in a surface area of 34 m² g⁻¹. This heat treatment allows eliminating synthesis residues (*i.e.* nitrate and ammonium ions), providing a

122 homogeneous specific surface and reproducible characteristics of the departing powder. Further, it
123 contributes to a more stable suspension and minimizing agglomeration between HA particles. Heat
124 treatment and SD processing did not affect the phase compositions, being the same of pure HA according
125 to diffraction pattern (Figure 2). As revealed on SEM images (Figure 3) and PSD curve (Figure 4) the nano-
126 sized HA particles (D50 value 0.13 μm) have a tendency to agglomerate, therefore, the suspension for SD
127 processing must be carefully prepared.

128
129 Figure 2 – XRD curves of pure HA treated at 650 °C for 0.5 h and SDHA treated at 1000 °C for 1 h.

130
131 Figure 3 – SEM-FEG images of heat-treated departing HA powder, indicating the tendency of the
132 agglomeration (left). Close-up of agglomerated nano-sized particles (right).

133
134 Figure 4 – PSD curve of heat-treated departing HA powder.

135 136 3.2. Effect of suspension formulation

137 Suspension composition has major importance because its characteristics will influence all the spray
138 drying process. For this step, the trial and error experimentation method is applicable when no information
139 is found in the literature. However, there are aspects of fundamental importance to be considered (*e.g.*
140 maximal solid content, slurry viscosity) that can be easily found in the related bibliography. Moreover,
141 machine manufacturers can provide elementary information about recommended processing
142 characteristics. Early trial and error experiments, together with literature information, have provided a
143 point of departure in terms of mixture preparation, solid content, binder selection, and processing
144 parameter values.

145 First, the binder selection must consider the powder's final application (in this case, bone tissue
146 applications). Therefore, after processing, it must maintain the original HA chemical composition. In
147 previous essays, the performance of different binders: corn starch (Roquette, ref: 764071),
148 polyvinylpyrrolidone (grade 30 and 90 from BASF), and methylcellulose (Methocel A15-LV Premium) were
149 analyzed. Methylcellulose demonstrated a larger average particle size, better process efficiency, and
150 requiring lower concentrations. Spray-dried HA (SDHA) powder, after heat treatment at 1000 °C for 1 h,
151 has matching phase compositions to heat-treated HA as shown in Figure 2, confirming the suitability of
152 methylcellulose in terms of not modifying powder composition.

153 Once the type of binder is selected, the amount of HA must be defined. Adding too much HA in the
154 suspension will prevent good homogeneity and induce solid deposition. Moreover, it will increase viscosity
155 and difficult spray drying processing (i.e. nozzle blocking). On the other hand, a low solid concentration will
156 result in a smaller particle size [35]. Previous essays indicated the use of around 20 wt% HA content for the
157 proposed screening method and particle size objectives. To guarantee suspension homogeneity, it is
158 recommended to agitate with a magnetic stirrer for at least 10 h before starting the spray drying process.
159 While processing, continuously stirring is required to maintain the mixture uniform and with constant
160 viscosity [36].

161 SD process is highly dependent on the suspension's characteristics and its viscosity has a great
162 influence on the obtained powder. As detailed in Figure 5, the amount of methylcellulose has a large effect
163 on the suspension's rheology. Table 2 provides the values obtained from the slurry rheological analysis,
164 Herschel–Bulkley model was used given its fitting with experimental results. Yield stress values were
165 similar between SD01-SD02 and SD03-SD04, indicating two types of behavior according to binder amount.
166 All the suspensions showed pseudoplastic shears thinning behavior, implicating in a viscosity decrease with
167 increasing shear rate. This is an important characteristic that guarantees suspension uniform viscosity
168 along with all the SD processing, under constant agitation. Large viscous forces will need more energy for
169 breaking the droplets, resulting in larger droplets [37]. This phenomenon was observed when processing
170 SD01, where occurred slurry droplets deposition in the drying chamber.

171 PSD analyses were performed for all suspensions (Figure 6). Although the suspensions have similar
172 dispersion curves, SD01 and SD02 indicate a larger volume of particles around 50 μm area, suggesting that
173 the suspension is not well homogenized. As detailed in Table 2, this bimodal distribution reflects the values
174 of D10, D50, D90, and its ratio. Particle size values of D10 mean that 10% of particles have smaller
175 diameters than the D10 value, in the same way, D50 and D90 represent the 50% and 90% portions. (D90-
176 D10)/D50 ratio provides information related to the particles' distribution width, in which, a wider
177 distribution is observed with high ratio values. The values obtained by (D90-D10)/D50 ratio enhance the
178 significant distribution behavior of SD01-SD02 versus SD03-SD04. It is possible that suspensions SD01 and
179 SD02 have not completely dissolved the binder, remaining agglomerates. Individual nano-sized HA particles
180 tend to gather together (Figure 3), accentuating agglomeration effects.

181 SEM images (Figure 7) suggest that the high amount of methylcellulose binder in suspensions SD01
182 and SD02 formed binder agglomerates in the particles, causing defects after sintering that can be observed
183 by the empty spaces in the particles (forming donut-like particles). Contrastingly, heat-treated SD04
184 powder presented some particles with an insufficient amount of binder, preventing proper cohesion
185 between HA departing particles (also evidenced by smaller values on PSD) and restricting the formation of
186 appropriate morphology.

187 According to rheological analysis and PSD values, SD03 and SD04 have shown the most suitable
188 results. When also considering morphological characteristics of spray-dried granules, SD04 did not have a
189 sufficient amount of binder to guarantee proper cohesion of nano-sized HA particles, therefore, SD03 was
190 chosen to proceed with the following steps.

191
192 Figure 5 – Viscosity measurements of HA suspensions SD01, SD02, SD03, and SD04.

193
194 Figure 6 – PSD curves of suspensions SD01, SD02, SD03, and SD04.

195

196 Table 2 – Rheological values obtained from the Herschel–Bulkley model and respective D10, D50, D90, and
197 ratio measures for HA suspensions.

198

199 Figure 7 – SEM images of HA particles from SD01, SD02, SD03, and SD04, after heat treatment at 1000 °C
200 for 1 h.

201

202 3.3. Effect of spray drying parameters

203 Nozzle cap position is important to avoid excessive droplets deposition on the drying chamber wall,
204 which can result in lower process efficiency. In order to verify any influence of spray width on the particle's
205 morphology, particle measurement and SEM images were conducted. Particle size distribution (Figure 8)
206 and morphology have shown to be similar between the nozzle's four positions (SD05 to SD08), hence,
207 these attributes were not directly affected by the changes in the spray angles, neither they were sufficient
208 to validate an optimal nozzle position.

209 Considering the similarity in morphology and particle size distribution, position II was chosen
210 because SD06 had around 5% more process yield (powder recover quantity) when compared to the others.

211

212 Figure 8 – PSD of HA densified particles (after heat treatment at 1000 °C for 1 h): SD05 (pos. I), SD06 (pos.
213 II), SD07 (pos. III), SD08 (pos. IV).

214

215 The final properties of spray-dried particles are highly dependent on processing parameters, as well
216 as equipment's features and configurations. Although it is possible to adjust particle characteristics by
217 changing the processing parameters, it is necessary to establish a suitable departing suspension to achieve

218 the targeted goals in terms of particle. Afterward, the heat treatment process will affect the particle
219 density, crystallinity, and mechanical integrity [38]. Considering that heat treatment is a post-process of
220 spray drying, not directly influencing the particle size distribution and morphology, it will not be
221 investigated here. In terms of particle-size distribution and process yield, key parameters are suspension's
222 solid content, spray drying slurry feed, and atomization pressure; yet, other factors like nozzle diameter,
223 inlet temperature, aspirator velocity, and drying gas humidity also influence the obtained particles
224 [25,38,39]. As mentioned before, an early trial and error method should be applied to comprehend the
225 basic correlations between all the processing factors. In-depth analysis for investigating the influence of
226 different processing variables should be done using statistical tools and it is recommended to perform at
227 least 3 replicates for establishing any conclusions.

228
229 Table 3 – Factorial design parameters and values and respective D10, D50, D90 mean size and size ratios,
230 after heat treatment at 1000 °C for 1 h. The (-) signal represents lower and (+) higher values of the two
231 levels factorial design.

232
233 Particle size information is displayed in Figure 8 and Table 3. It has been reported in the related
234 bibliography that a higher atomization pressure decreases the particle size [35,38,40]. This observation is
235 in accordance with our results, when comparing SD09 and SD11 (same slurry feed and SD11 with higher
236 atomization pressure), SD11 possesses lower particle values for D10 and D50. In the same manner, SD12
237 has D10, D50, and D90 particle size lower than SD10 (same slurry feed and SD12 with higher atomization
238 pressure). On the other hand, from our results, it was not possible to observe the association between
239 larger particle sizes with increases in slurry feed rate reported in the literature [38,40]. Analyzing the
240 curves in Figure 9, it can be observed similarities between SD09-SD10 and SD11-SD12, this might indicate a
241 minor influence of slurry feed in our experiences. Probably, a greater difference between slurry feed values
242 would evidence variances in particle size. Nevertheless, it is important to highlight that these comparisons

243 are only illustrative, for representative conclusions it would be necessary more replicates, experimental
244 error determination, and the use of statistical analysis of variance (ANOVA). SEM images (Figure 10) have
245 shown similar spherical morphology for the respecting spray-dried powder and, as expected, a greater
246 population of bigger particles were observed on SD09 and SD10.

247
248 Figure 9 – PSD dispersions of HA particles SD09, SD10, SD11, SD12, after heat treatment at 1000 °C for 1 h.

249
250 Figure 10 – SEM images of HA particles SD09, SD10, SD11, and SD12, heat-treated at 1000 °C for 1 h.

251
252 Introducing satisfaction index for the responses D50, (D90-D10)/D50 and particle morphology,
253 desirability values were obtained (Table 4). Individual desirability of D50 and morphology were calculated
254 using $\mathcal{D} = (Y_i - L)/(T - L)$ equation, where Y_i is the response, L the lower value, and T the target value.
255 Conversely, for (D90-D10)/D50 desirability a minimized result was targeted, therefore, $\mathcal{D} = (U -$
256 $Y_i)/(U - T)$ equation was used (U means upper value). The applied ranges of values were: i) D50: 100%
257 desirability if value greater than 25 and 0% desirability if value less than 15; ii) (D90-D10)/D50: 100%
258 desirability if value less than 1 and 0% desirability if value greater than 3; iii) particle morphology: 100%
259 desirability if value greater than 5, 0% desirability if value less than 1. For particle morphology, SEM images
260 were analyzed and for each sample, it was given a 1 to 5 score (5 is the most suitable morphology). Higher
261 values of desirability were observed on SD09 and SD10 mainly due to D50 and (D90-D10)/D50.

262 Although global desirability pointed out SD09 and SD10 as the most suitable powder characteristics,
263 all SD powders achieved the proposed morphology and size objectives. The variation of two processing
264 parameters has shown the capability of adjusting particle size characteristics.

265
266 Table 4 – Samples and respective desirability responses.

267

268 4. Conclusions

269 This screening method contemplates the main steps for powder preparation suitable for SLS. Spray-
270 dried HA particles were successfully produced within the proposed morphology. Binder and HA content of
271 the departing slurry have an important effect on viscosity. Therefore, special attention must be given to
272 preparing the departing suspension. Variations on spray drying processing parameters have shown the
273 possibility of tailoring particle size and distribution. For a proper analysis of the processing parameters
274 variation, statistical tools must be used. PSD and SEM images have indicated suitable particle
275 characteristics for SLS processing, although additional studies must be conducted to confirm SLS
276 processability. The versatility of the proposed method makes it possible to be applied in other bioceramic
277 materials and types of binders, targeting different particle sizes.

278

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288

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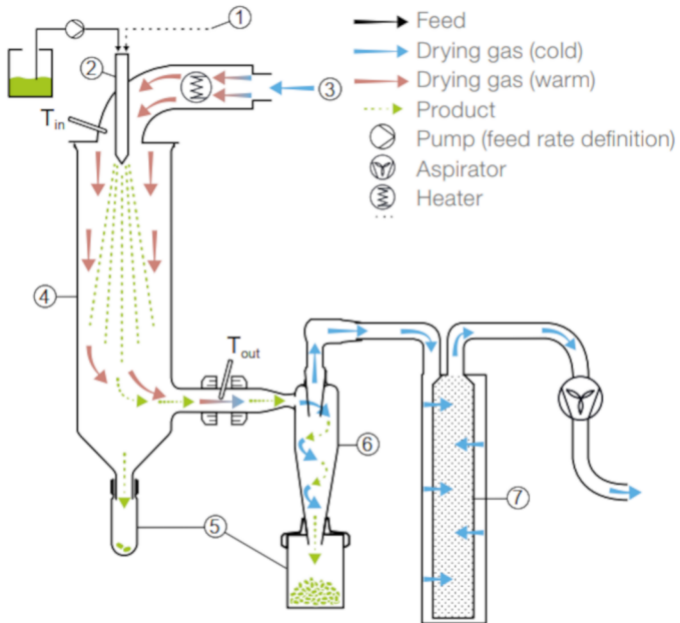
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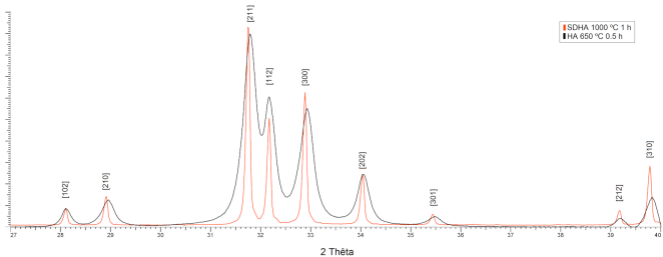
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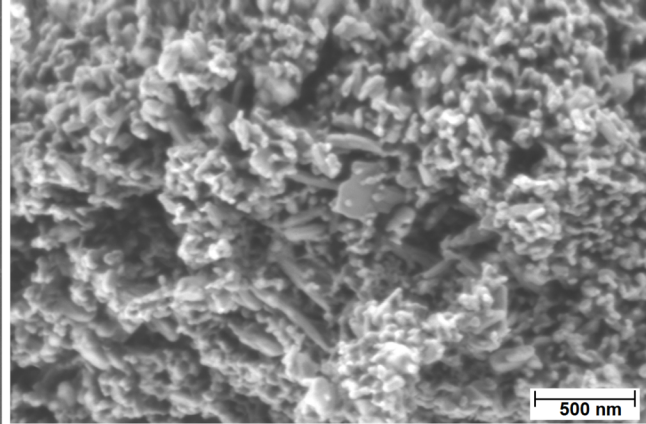
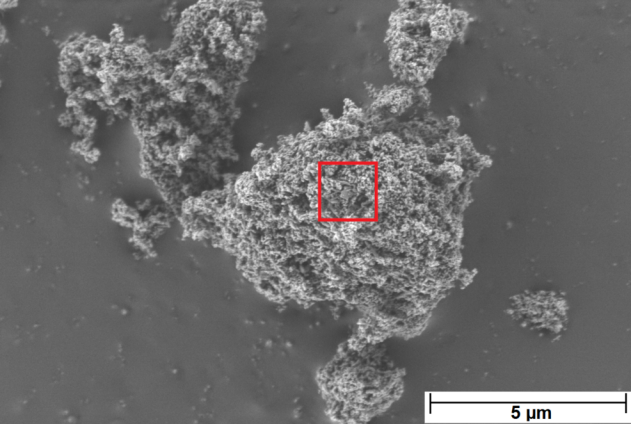
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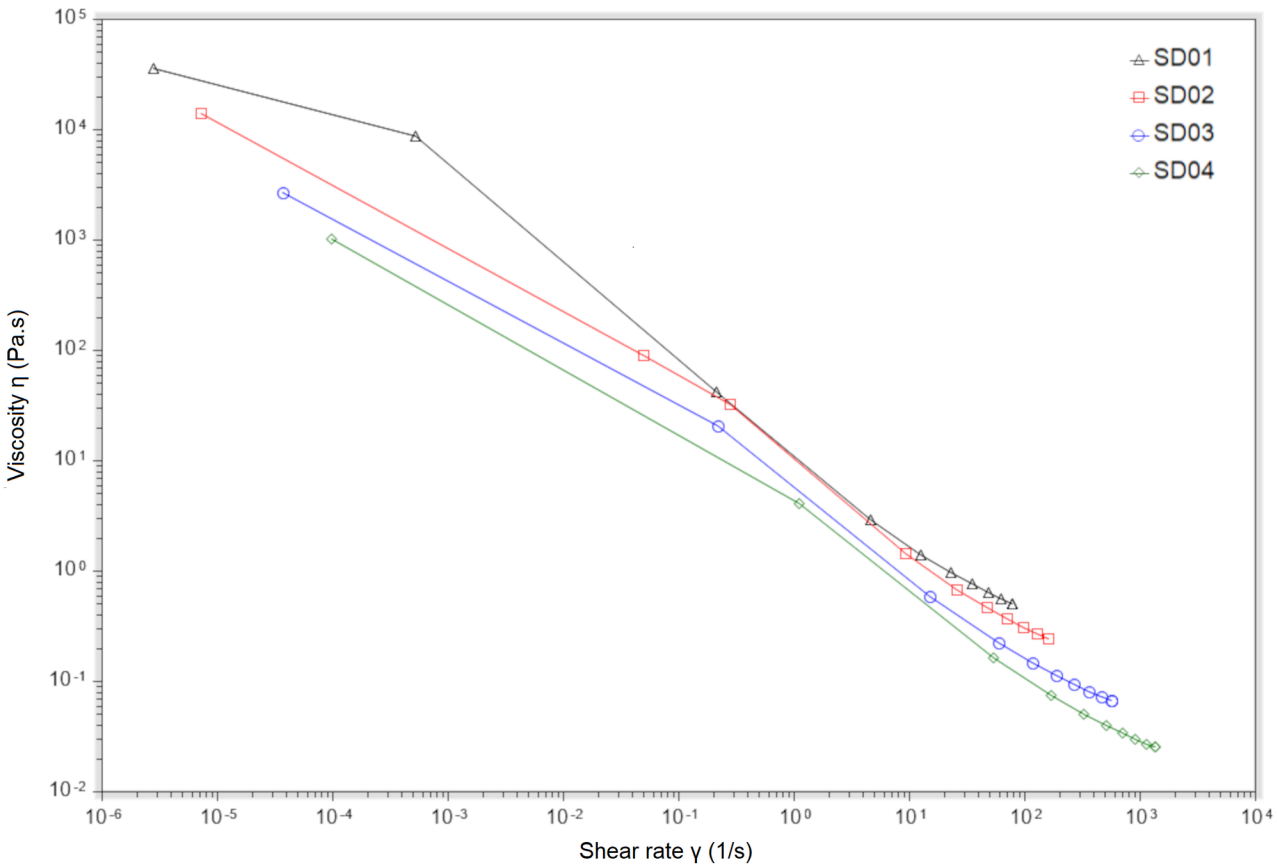


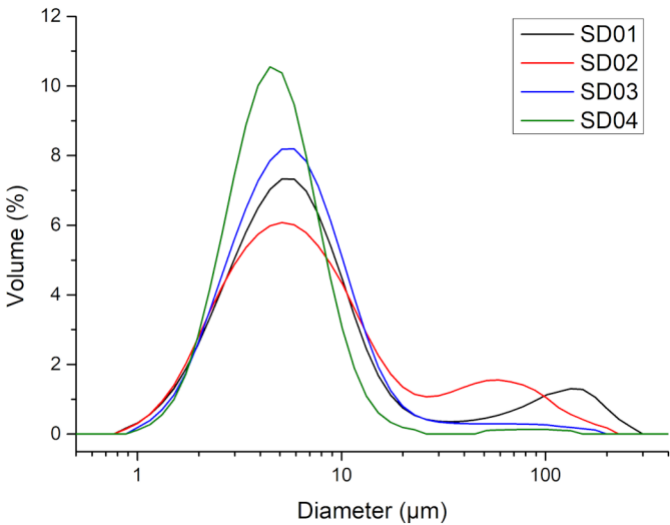
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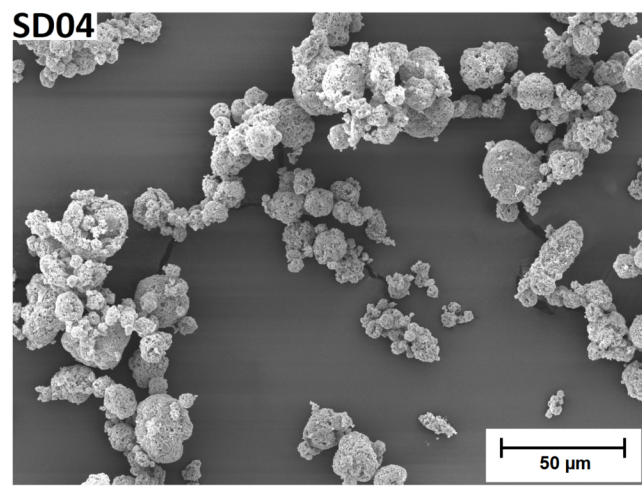
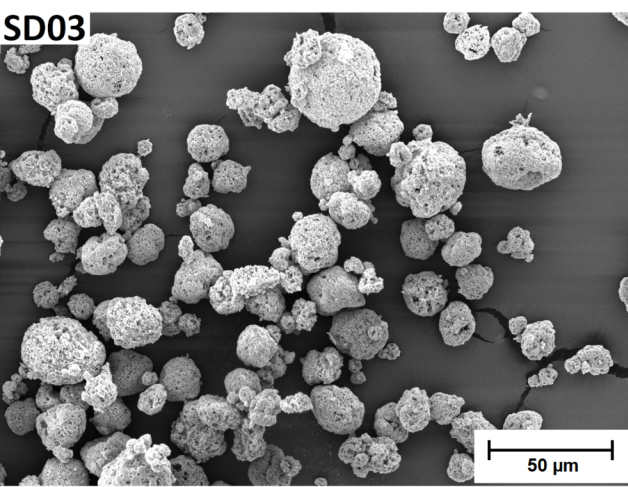
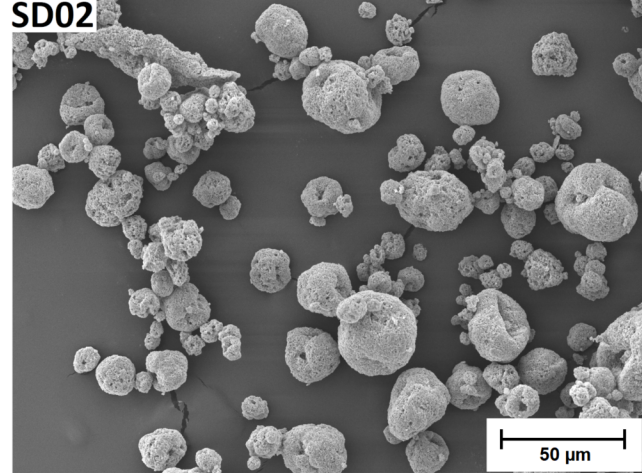
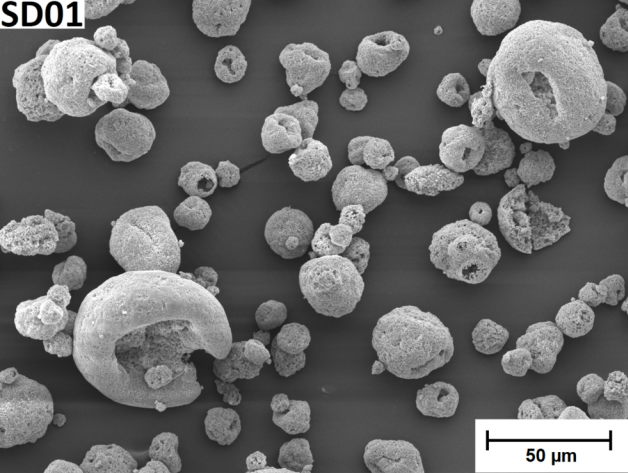


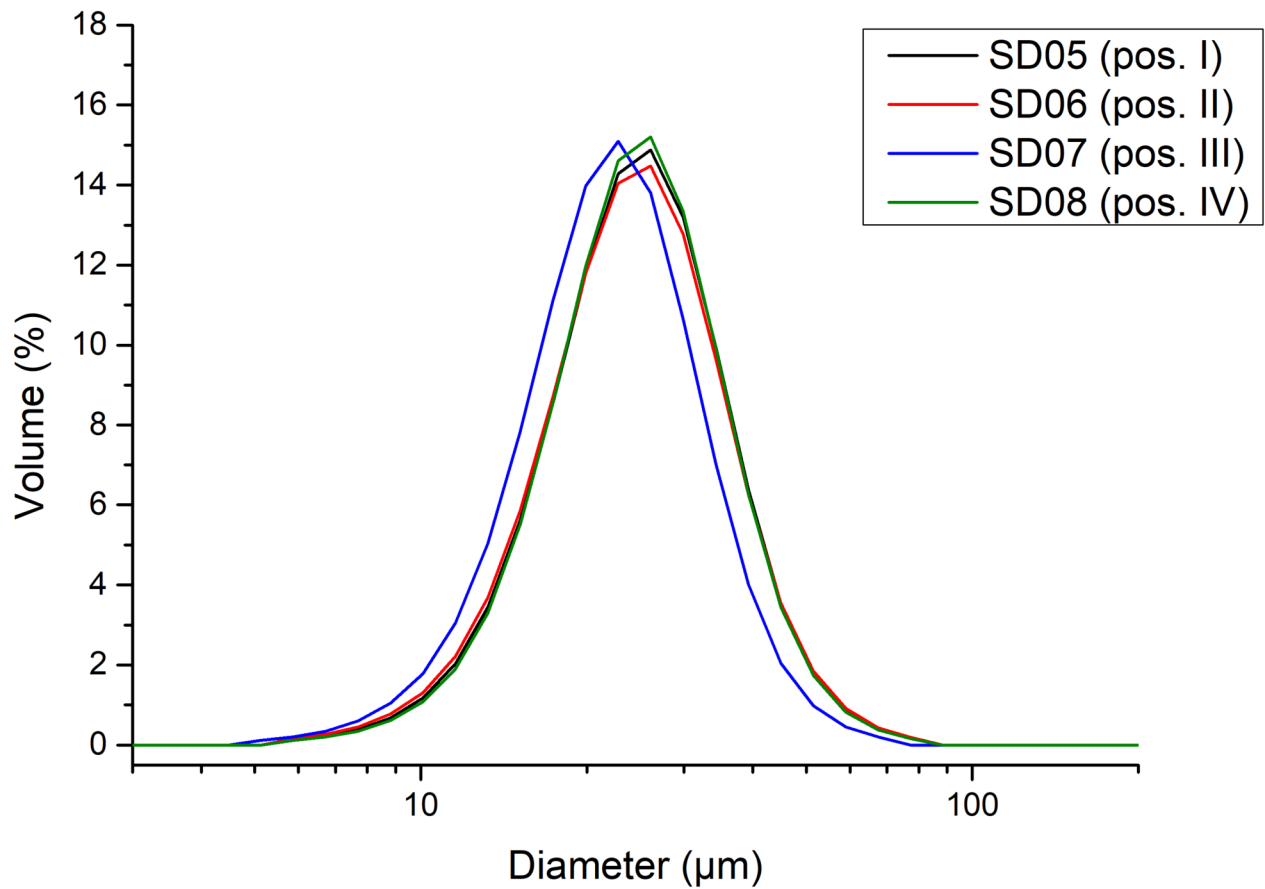


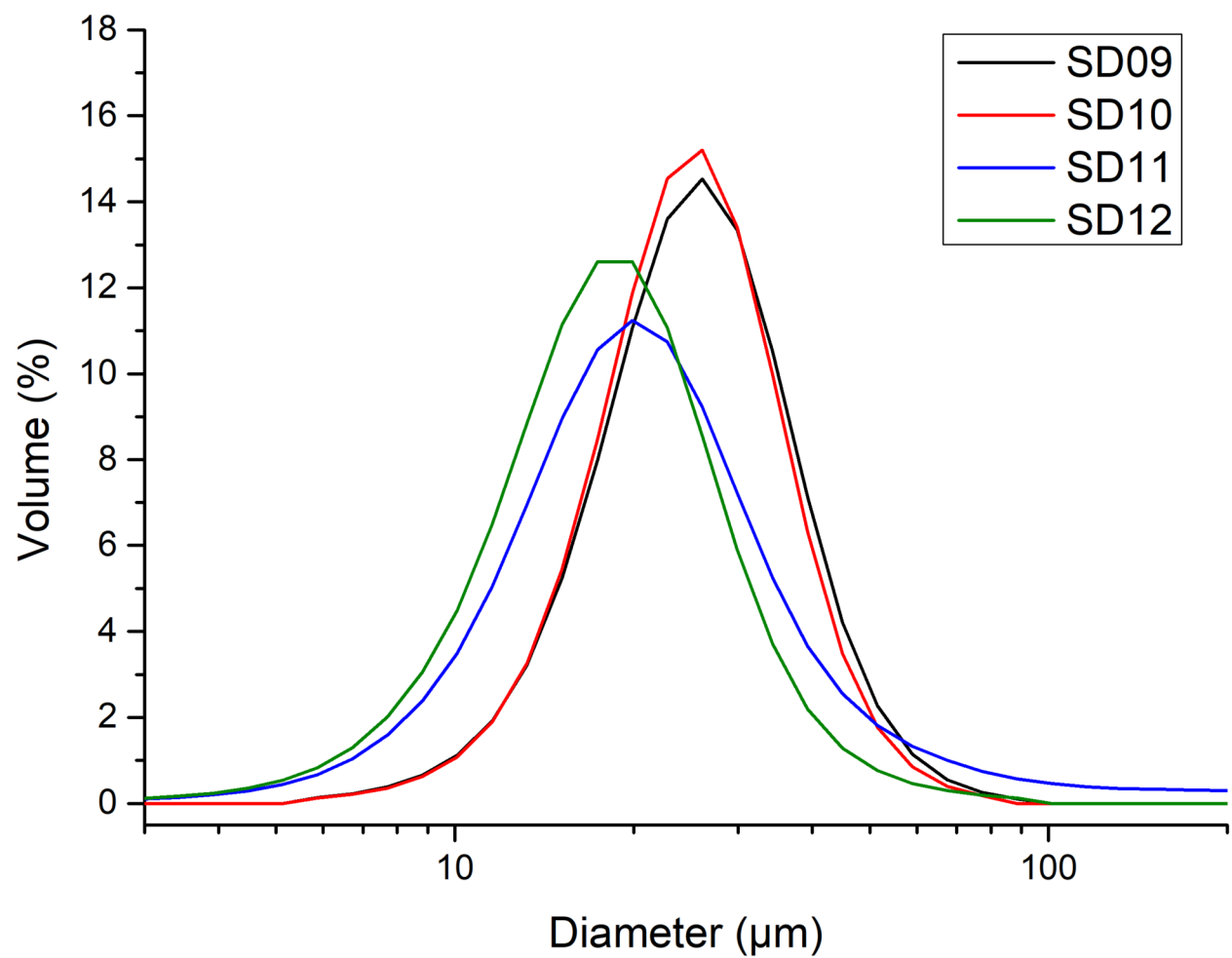












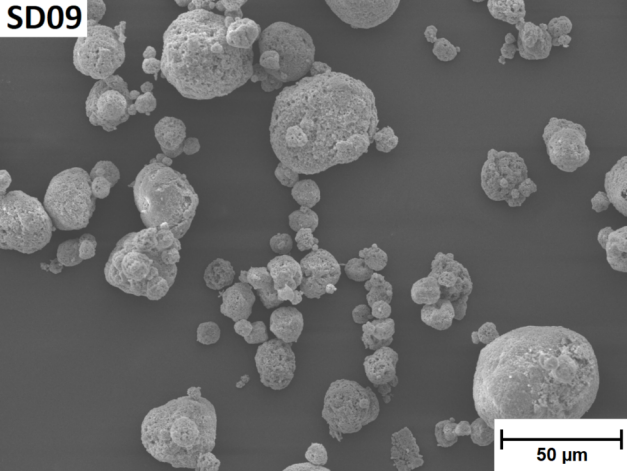
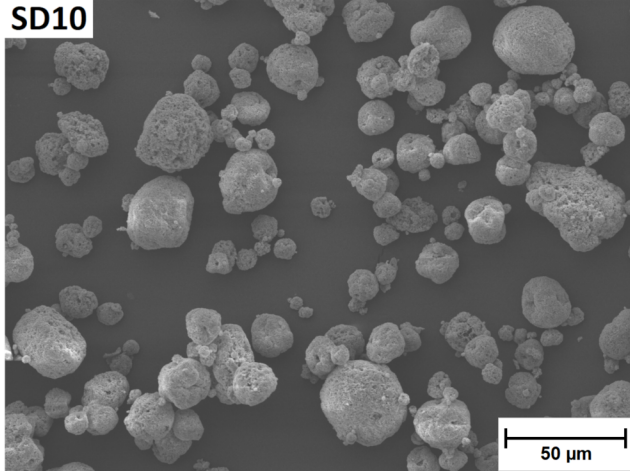
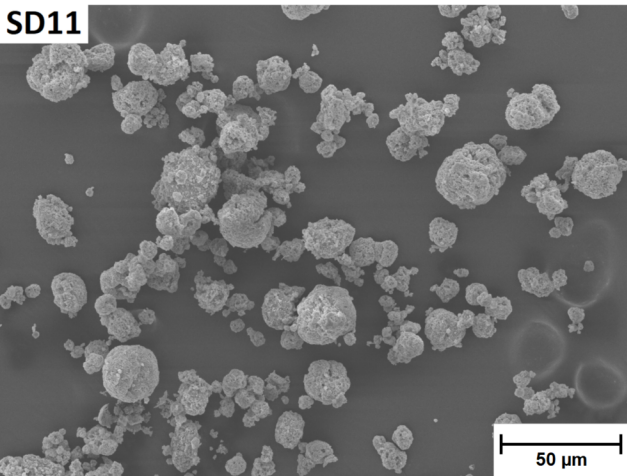
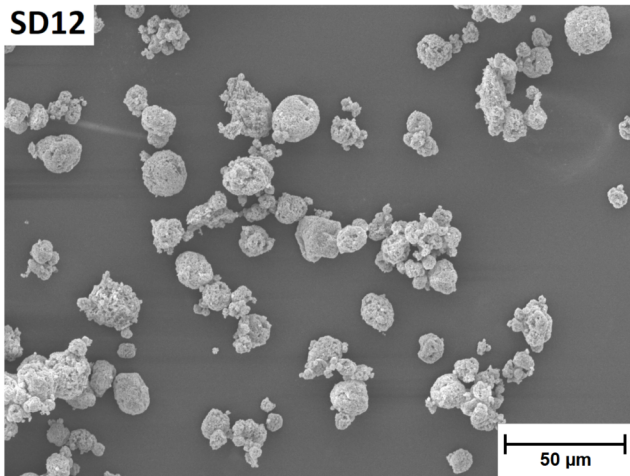
SD09**SD10****SD11****SD12**

Table 1 – Compositions of spray-drying HA aqueous suspensions.

| Sample | Hydroxyapatite (wt%) | Methylcellulose (wt%) | Deionized water (wt%) |
|--------|----------------------|-----------------------|-----------------------|
| SD01 | 20.00 | 3.20 | 76.80 |
| SD02 | 20.16 | 2.42 | 77.42 |
| SD03 | 20.32 | 1.63 | 78.05 |
| SD04 | 20.49 | 0.82 | 78.69 |

Table 2 – Rheological values obtained from the Herschel–Bulkley model and respective D10, D50, D90 and ratios measures for HA suspensions.

| Sample | Yield Stress (Pa) | Viscosity (Pa·s) | Rate index | D10 (µm) | D50 (µm) | D90 (µm) | (D90-D10)/D50 (µm) |
|--------|-------------------|------------------|------------|----------|----------|----------|--------------------|
| SD01 | 8.47 | 1.70 | 0.67 | 2.18 | 5.43 | 55.65 | 23.08 |
| SD02 | 8.56 | 1.07 | 0.66 | 2.13 | 5.88 | 46.99 | 19.32 |
| SD03 | 5.91 | 0.51 | 0.65 | 2.24 | 5.10 | 12.42 | 3.26 |
| SD04 | 5.92 | 0.18 | 0.70 | 2.22 | 4.29 | 8.36 | 1.83 |

Table 3 – Factorial design parameters and values and respective D10, D50, D90 mean size and size ratios, after heat treatment at 1000 °C for 1 h. The (-) signal represents lower and (+) higher values of the two levels factorial design.

| Run | Sample | Atomization pressure (mmHg) | Slurry feed (mL min ⁻¹) | D10 (µm) | D50 (µm) | D90 (µm) | (D90-D10)/D50 (µm) |
|-----|--------|-----------------------------|-------------------------------------|----------|----------|----------|--------------------|
| 1 | SD09 | 45 (-) | 21.00 (-) | 13.92 | 23.67 | 38.15 | 1.04 |
| 2 | SD10 | 45(-) | 25.50 (+) | 13.90 | 23.12 | 36.53 | 0.96 |
| 3 | SD11 | 60 (+) | 21.00 (-) | 9.71 | 19.02 | 39.52 | 2.11 |
| 4 | SD12 | 60 (+) | 25.50 (+) | 9.01 | 16.85 | 29.24 | 1.37 |

Table 4 – Factorial design parameters and values and respective D10, D50, D90 mean size and

| Sample | Analyzed responses | | | Individual desirability | | | Global desirability |
|--------|--------------------|--------------------|---------------------|-------------------------|---------------|---------------------|---------------------|
| | D50 (µm) | (D90-D10)/D50 (µm) | Particle morphology | D50 | (D90-D10)/D50 | Particle morphology | |
| SD09 | 23.67 | 1.04 | 4 | 86.70% | 97.33% | 75.00% | 85.86% |
| SD10 | 23.12 | 0.96 | 4 | 81.20% | 100.00% | 75.00% | 84.76% |
| SD11 | 19.02 | 2.11 | 3 | 40.20% | 26.00% | 50.00% | 37.39% |
| SD12 | 16.85 | 1.37 | 3 | 18.50% | 75.33% | 50.00% | 41.15% |

