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Comparison of low-shear and high-shear granulation processes: effect on implantable calcium phosphate granule properties

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Abstract

Background: Calcium phosphate porous ceramics present a great interest not only as complex bone defect fillers but also as drug delivery systems. Most of the methods described in the literature to fabricate pellets are based on compaction, casting into spherical molds, or on processes such as liquid immiscibility or foaming. Despite wet granulation is used in a wide range of applications in pharmaceuticals, food, detergents, fertilizers, and minerals, it is not applied in the biomaterial field to produce granules. **Methods:** In this study physicochemical and in vitro drug delivery properties of implantable calcium phosphate granules, produced by two wet agglomeration processes, were compared. Pellets obtained by high shear granulation (granulation in a Mi-Pro apparatus) were shown to be more spherical and less friable than granules elaborated by low shear process (granulation in a Kenwood apparatus). Although Mi-Pro pellets had a slightly lower porosity compared to Kenwood granules, ibuprofen loading efficiency and dissolution profiles were not statistically different and the release mechanism was mainly controlled by diffusion, in both cases. **Conclusion:** Mi-Pro pellets appeared to be better candidates as bone defect fillers and local drug delivery systems as far as they were more spherical and less friable than Kenwood agglomerates.

Key words: Bioceramics; bone filling; calcium phosphate; dissolution; high-shear process; ibuprofen; low-shear process; physicochemical properties; porosity; wet granulation

Introduction

Calcium phosphate porous ceramics present an interesting challenge in the biomaterial field for bone substitution¹⁻³ as well as for drug release⁴⁻⁷. In fact, the controlled porosity allows targeting the drug directly to the site by a local, continuous, and controlled flux over a long period of time⁸. The microporosity, consisting of pores smaller than 10 μm in diameter, allows this slow release of the loaded drug⁹. For bone substitution, implants with an additional larger porosity, that is, macroporosity, are expected to promote the biological integration, especially bone ingrowth¹⁰⁻¹⁴. Hulbert et al.¹⁵ indicate that macropores larger than 100 μm in diameter are required to host cellular and extracellular

components of bone and blood vessels and greater than 200 μm in diameter to be effective in osteoconduction. Nevertheless, there is an obligation to find a compromise between porosity and sufficient mechanical strength.

Among the ceramic physical presentations that are developed, blocks are often highly porous due to the addition of a template further removed. Porosity is thus created before implantation, ensuring bone colonization into defect cavities. However, they are not suitable for complex-shaped bone defect filling^{13,16,17}. Bone substitutes such as cements are well adapted to complex-shaped cavities because they are in a casting step and harden in situ, but in most cases they present usually pores in the nano-/micrometer range¹⁸⁻²⁰. Only few studies describe the creation of macroporosity in situ by the pore former

dissolution into the bone cavity²¹⁻²³. More recently, injectable bone substitutes were developed. They are well adapted to all cavity shapes, and, as for cements, macroporosity is created in situ by the biodegradation of the water-soluble polymer used as ceramic granule carrier²⁴. In the last two cases, bone colonization depends on the macropore creation kinetics. Therefore, the development of calcium phosphate pellets is of great interest as this presentation can fill all defect cavities with an initial macroporosity resulting from intergranule spaces.

Pellets described in the literature are generally prepared by compaction^{25,26}, by casting into spherical molds^{27,28} or by innovative processes (liquid immiscibility, foaming)^{17,29-31}. Nevertheless, despite granulation is a process widely used in a wide range of industrial applications such as pharmaceuticals, food, detergents, fertilizers, and mineral processing^{32,33}, it is not applied in the biomaterial field to produce granules.

Wet granulation is a size enlargement process consisting in the agglomeration of powder particles by spraying a liquid binder while particles are agitated by specific devices in order to produce large agglomerates, usually termed granules^{32,33-35}. The binder solution can also be obtained into the bowl by adding the granulation liquid on the mix containing the binder in a solid form. Size enlargement is often intended to ensure the formulation homogeneity, improve the flow properties, reduce the dustiness, and control the dissolution rate³⁶. Granulation process is commonly described as a combination of three steps³⁶⁻³⁹:

- wetting and nucleation, where the liquid binder is brought to the dry powder mix and nuclei are formed;
- consolidation and growth, where collisions between granules and powder particles induce granule growth and compaction; and
- attrition and breakage, where granules may be broken due to impacts against other granules or equipment.

These phenomena control the final characteristics of the granules and are influenced by the equipment type, its size, and the process parameters⁴⁰. Spheronization can be performed before drying in order to produce spherical pellets.

Wet granulation can be achieved by several techniques⁴¹⁻⁴⁴. This work considers low-shear and high-shear granulation for calcium phosphate pellet elaboration. Low-shear mixers are commonly used in the pharmaceutical industry for dry or solid-liquid mixing⁴⁵. Moreover, they are ideal on a laboratory scale. In this work, low-shear wet granulation was performed by using a Kenwood planetary mixer (Kenwood Ltd., Hampshire, UK) composed of a stainless steel bowl and a K-beater-type agitator that rotates simultaneously around two vertical axes. After mixing and spraying the granulation liquid, the wetted mass is forced through the sieve of an oscillating

granulator to produce granules that are finally dried. High-shear mixers are interesting because they allow dry mixing, wetting, granulation, and sometimes drying to be performed in the same apparatus. Moreover, granules thus obtained are generally more spherical and better compacted due to the impact of the impeller and the collisions with the wall and with the other pellets⁴⁶. In this study, high-shear granulation was carried out in a laboratory-scale mixer-granulator Mi-Pro (Pro-C-epT, Zelzate, Belgium) consisting of a glass bowl, an impeller, and a chopper. In both granulation processes, dry pregelatinized starch was introduced in the bowl, and the binder solution was obtained when distilled water was added.

This study investigates the ability of low-shear and high-shear granulation to prepare calcium phosphate granules intended for bone implantation. In order to attempt the porosity requirements described previously, both types of granules are submitted to a thermal treatment creating porosity by removal of the granulation binder thus acting as a pore former. Porous granules thus obtained are finally loaded with ibuprofen, an anti-inflammatory agent, to be used as drug delivery systems. The impacts of the granulation process on physicochemical and dissolution properties of the loaded granules were compared in order to select the more suitable granulation process.

Materials and methods

Granulation processes

Calcium phosphate powder (CaP, batch number G8138/3, Cooper, Melun, France), used as a granule skeleton, was granulated with 10% pregelatinized starch (Sepistab ST 200, batch number 80551; Seppic, Paris, France) used as a binder (Figure 1) according to the granulation processes described below. Granules thus obtained were dried in a fluidized bed (Glatt, Haltingen-Binzen/Baden, Germany) during 20 minutes at 60°C and sieved in order to retain the (710–1000 µm) fraction. Based on a previous thermogravimetric analysis⁴⁷, these granules were then submitted to a heat treatment, that is, calcination (Kanthal Super, Rapid High Temperature Furnace; Bulten-Kanthal, Hallstahammar, Sweden) in order to create porosity by removal of the binder, thus acting as a pore former. In the first step of this treatment, pellets were heated at 270°C with a heating rate of 2°C/min and maintained at this temperature for 2 hours in order to burn out the pregelatinized starch. In a second step, they were heated at the same heating rate, up to 900°C. This temperature was kept constant for 15 minutes before cooling at the rate of 10°C/min. Finally, granules were loaded with ibuprofen at 36%, by a solvent evaporation method from an ethanolic ibuprofen solution (Ibuprofen

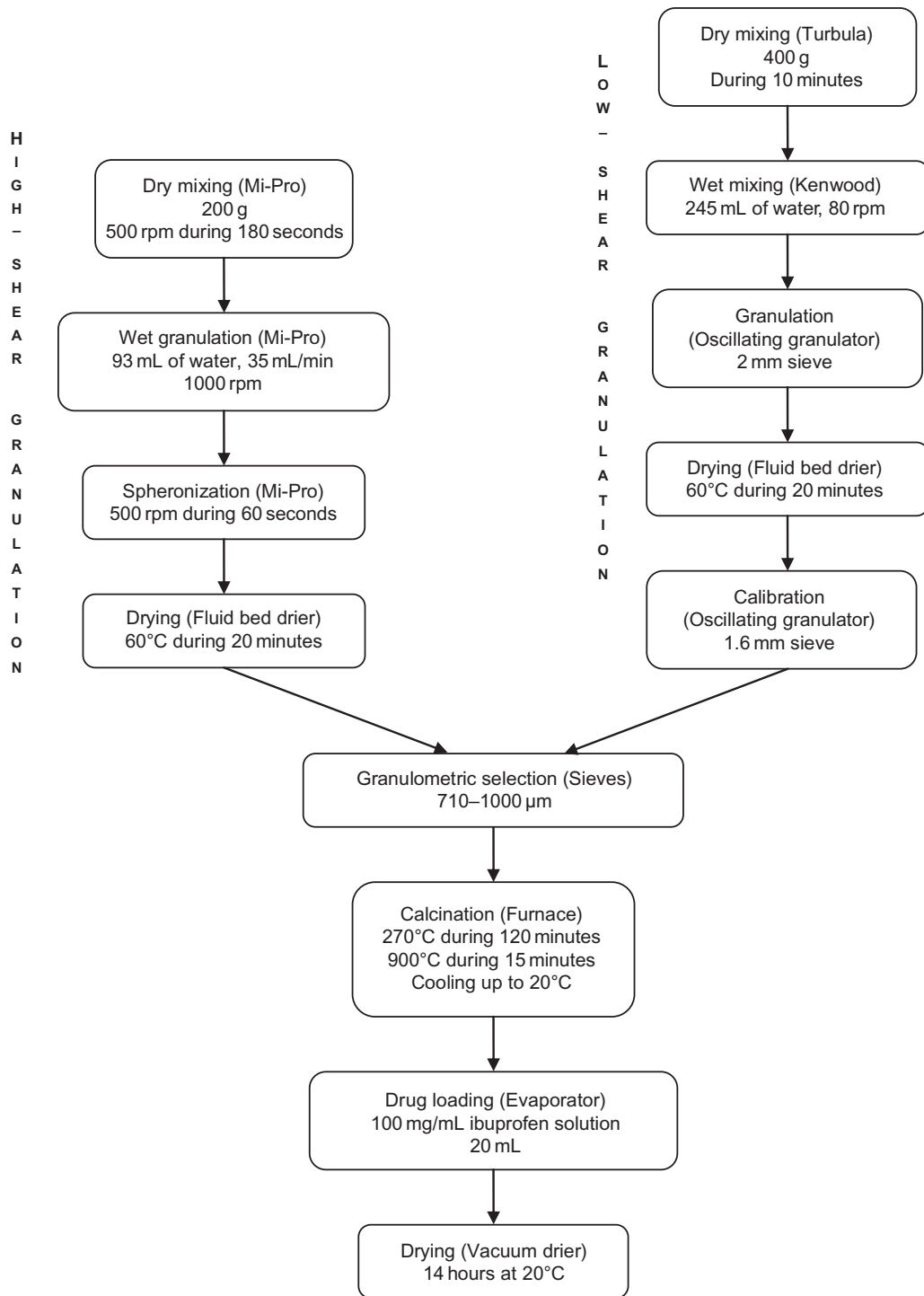


Figure 1. Steps of the loaded porous pellet fabrication processes using high- or low-shear granulation.

50, batch number IB1M738; BASF, Ludwigshafen, Germany) in a Rotavapor (Büchi, Flawil, Switzerland)⁴⁷.

Two wet granulation processes were compared in this study:

- First, agglomerates were produced by a multiphasic low-shear process. CaP (360 g) and ST 200 (40 g) were

uniformly mixed in a Turbula (type T2C, Basel, Switzerland) during 10 minutes. Then, the mix was poured into the stainless steel bowl of a Kenwood planetary mixer (model Kenwood Chef KM201, Kenwood Ltd.) and wet with 245 mL distilled water. Finally, powder was granulated using an oscillating granulator (Erweka AR 400 type FGS; Erweka

Apparatebau GmbH, Heusenstamm, Germany) equipped with a 2 mm sieve prior to calibration of the dried granules using a 1.6 mm sieve. These granules are referred to as Kenwood granules thereafter.

- Secondly, CaP (180 g) and ST20 (20 g) were mixed during 180 seconds in a Mi-Pro high-shear granulator (Pro-C-epT) equipped with a three-blade impeller and a chopper, both rotating at 500 rpm. Then, the mix was granulated with 93 mL water, added at a distribution rate of 35 mL/min, with impeller and chopper speeds of 1000 rpm. Finally, granules thus obtained were spheronized during 60 seconds at 500 rpm for impeller and chopper speeds^{47,48}. They are referred to as Mi-Pro pellets thereafter.

Physicochemical characterization of unloaded granules

The methods described in this part were carried out both on uncalcined and calcined granules.

Granule morphology was observed by scanning electron microscopy (SEM) (Stereoscan S260, Leica, Cambridge, UK) and the circularity coefficient was determined from optical microscopy (MZ 16, Leica). Twenty granules out of each batch were analyzed by the Image J software (<http://rsb.info.nih.gov/ij/>).

Pycnometric density (d_{pycno} , g/cm³) was determined using a helium pycnometer AccuPyc 1330 (Micromeritics Instruments Inc., Norcross, GA, USA)⁴⁹. Prior to evaluation, samples were degassed for 3 days at room temperature at a pressure less than 50 mTorr (VacPrep 061, Micromeritics Instruments Inc.). Measurements were repeated until stabilization.

Specific surface area (S_{spe} , m²/g) was measured by nitrogen adsorption using a Gemini 2360 Analyser (Micromeritics Instruments Inc.) and calculated according to the Brunauer–Emmet–Teller equation⁵⁰. Samples were previously degassed under the same conditions as for pycnometric density measurements.

Bulk (d_{bulk} , g/cm³) and packed (d_{packed} , g/cm³) densities were determined in triplicate using a 1 cm³ cell, according to

$$d_{\text{bulk}} = \frac{m}{V_0} \quad (1)$$

$$d_{\text{packed}} = \frac{m}{V_{0.5}}, \quad (2)$$

where m is the mass of granules freely poured into the cell, V_0 is the corresponding volume (1 cm³), and $V_{0.5}$ is the volume occupied by the granules under a 0.5 MPa uniaxial pressure (Lloyd Instrument LR30K, Fareham,

UK). This pressure corresponds to the packing and slippage of particles without any particle deformation⁵¹.

Friability measurement⁵² was performed in triplicate by introducing 10 g of granules into a glass container, which was subjected to horizontal oscillations (240 oscillations per minute during 240 seconds) in an oscillating apparatus (Friabimat, GTA-120; Erweka, Heusenstamm, Germany). After sieving on a 710- μm sieve to remove fine particles, granules were weighed and friability (F , %) was calculated according to the following formula:

$$F(\%) = \frac{m_1 - m_2}{m_1} \times 100, \quad (3)$$

where m_1 is the mass of granules before the test (10 g) and m_2 is the mass of granules retained by the sieve after the test.

Porosity measurements were carried out using a mercury intrusion porosimeter (Autopore IV 9500; Micromeritics Instruments Inc.) equipped with a 5 cm³ powder penetrometer. Cumulative and incremental mercury intrusion volumes were recorded. The intrusion volume V_{intra} (mL/g) corresponding to pellet porosity was deduced and associated with the corresponding pore size diameters.

Pellet porosity (%) was calculated according to

$$\text{Pellet porosity (\%)} = \frac{V_{\text{intra}}}{V_{\text{solid}} + V_{\text{intra}}} \times 100, \quad (4)$$

where V_{solid} was the solid granule volume, determined from the pycnometric density.

Characterization of drug-loaded granules

In vitro ibuprofen release studies from both types of granules were performed in triplicate in a paddle apparatus (USP Apparatus 2, Prolabo Dissolution Tester, Paris, France) equipped with a paddle stirrer rotating at 100 rpm, using 500 mL of phosphate buffer solution (pH 7.48) at 37°C as dissolution medium. About 3 mL buffer was withdrawn at regular intervals up to 300 minutes, and ibuprofen quantity was determined using a UV-Vis spectrophotometer (Uvikon 930, Kontron Instrument, Montigny-Le-Bretonneux, France) at 264 nm, corresponding to the wavelength of maximal ibuprofen absorption.

Dissolution profiles, that is, cumulative percentage of released ibuprofen (Q , %) versus time (t , minutes), were plotted for both types of granules.

The drug content was expressed by

$$\text{DC (\%)} = \frac{\text{experimental ibuprofen quantity}}{\text{sample mass}} \times 100. \quad (5)$$

Drug-loading efficiency (DLE) was calculated according to

$$\text{DLE (\%)} = \frac{\text{experimental ibuprofen quantity}}{\text{theoretical ibuprofen quantity}} \times 100, \quad (6)$$

where the theoretical ibuprofen quantity corresponded to 36% of the sample mass.

Dissolution profiles were analyzed according to the Weibull equation⁵³ in order to determine the characteristic dissolution time TW 80% (i.e., the time necessary to dissolve 80% of the drug substance).

Then, in order to study the effect of agglomeration process on granule properties, dissolution kinetics were compared using difference (*f1*) and similarity (*f2*) factors⁵⁴. Two dissolution profiles are considered as similar when *f1* is not greater than 15 and *f2* varies from 50 to 100. At least three time points, with only one greater than 85%, are necessary to apply the pairwise procedure^{55,56}.

Finally, in order to determine the release mechanism, results were fitted to two mathematical models, characterizing diffusion and erosion prevalence, respectively, the Higuchi equation⁵⁷:

$$Q(\%) = at^{1/2} + b, \quad (7)$$

where *a* is the release rate (%/min^{1/2}) and *b* a constant; and the Hixson-Crowell model⁵⁸:

$$\sqrt[3]{100} - \sqrt[3]{100 - Q} = ct, \quad (8)$$

where *c* is the release rate.

Finally, the Kopcha equation was used in order to confirm the release mechanism and to quantify the contributions of diffusion (*A*) and erosion (*B*)⁵⁹:

$$M = A\sqrt{t} + Bt. \quad (9)$$

From this equation, the ratio *A/B* was calculated and three situations may be observed. In the case of ratio *A/B* = 1, release mechanism is equally controlled by diffusion and erosion, if *A/B* > 1, diffusion prevails while if *A/B* < 1 erosion predominates.

Results and discussion

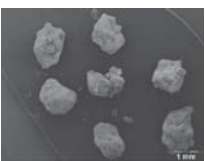
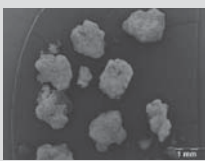
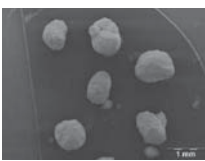
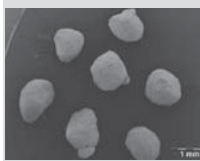
Effect of granulation process on granule physicochemical properties

The physicochemical characteristics of Kenwood and Mi-Pro granules before and after heat treatment are listed in Table 1.

SEM observations showed that Kenwood granules looked rougher and less spherical than Mi-Pro pellets. The lower sphericity was confirmed by their lower circularity coefficient. Circularity coefficients were unchanged after heat treatment and the Mi-Pro pellet sphericity was preserved (Table 1).

Pycnometric density highlighted the homogenous composition of the granules regardless of the granulation process. The experimental values of uncalcined granules were close to the theoretical density (2.68 g/cm³) of the CaP-starch mix that was calculated from the experimental values: 1.49 g/cm³ for pregelatinized starch and 3.04 g/cm³ for CaP, respectively, according to the theoretical composition. The heat treatment resulted in both removal of the pore former⁴⁷ and chemical modifications

Table 1. Effect of the granulation process on unloaded granule physicochemical properties.

	Kenwood		Mi-Pro	
	Before heating	After heating	Before heating	After heating
Morphology				
Circularity coefficient	0.79	0.76	0.83	0.83
<i>d</i> _{pycno} (g/cm ³)	2.70	3.04	2.70	3.04
<i>S</i> _{spe} (m ² /g)	34.96	5.91	33.35	5.69
<i>d</i> _{bulk} (g/cm ³)	0.58	0.55	0.73	0.71
<i>d</i> _{packed} (g/cm ³)	0.82	0.79	0.80	0.78
Friability (%)	20.7	21.3	6.7	12.1
Pellet pore size diameter range (nm)	(5-155) (155-1000)	(90-5000)	(5-150) (150-1000)	(90-400) (400-5000)
Pellet porosity (%)	54.4	61.2	47.9	57.7

by improving the coalescence of the elementary particles⁶⁰. In fact, calcium phosphate used as raw material was a biphasic component. Thermogravimetric analyses performed in a previous study⁴⁷ showed that the initial biphasic CaP became a monophasic component (β -TCP) after heat treatment. The measured pycnometric density confirmed these modifications, which was close to the theoretical β -TCP value (3.04 versus 3.07 g/cm³). Furthermore, Kenwood and Mi-Pro granule densities were similar confirming that heat treatment led to a similar CaP matrix whatever the granulation process (Table 1).

Uncalcined granules, obtained by both granulation processes, exhibited a high specific surface area (33.35 m²/g for Mi-Pro pellets and 34.96 m²/g for Kenwood granules, respectively). Specific surface area strongly decreased after heating (about 85%) despite removal of the pore former which created porosity. Raynaud et al.⁶¹ previously attributed this phenomenon to elementary particle coalescence without shrinkage. Specific surface area was 4% higher for Kenwood granules compared to Mi-Pro pellets, both before and after calcination, indicating that heat treatment maintained the difference induced by the granulation process on granule properties. This textural difference observed between low-shear and high-shear granules confirmed Shiromani and Clair's observations⁶². Moreover, the higher values were also in accordance with the higher roughness and the lower sphericity of Kenwood granules.

Bulk density also differentiated the two granule types. Mi-Pro high-shear granulation conferred a higher bulk density to the granule bed (0.73 versus 0.58 g/cm³) (Table 1). This difference, maintained after heat treatment (0.71 and 0.55 g/cm³, respectively), could be attributed to Mi-Pro pellet morphology that induced an easier initial packing. Despite this slight difference in bulk densities, Kenwood and Mi-Pro granules had close-packed densities, indicating that the same compacity might be reached at low pressure (0.5 MPa). These results differed from conclusions of Sheskey and Williams⁶³. In fact, their work indicated that granules produced either in a Kitchen Aid planetary mixer or in a Glatt Powrex high-shear granulator presented close apparent densities. This difference might be explained by the design of the apparatuses used in their study.

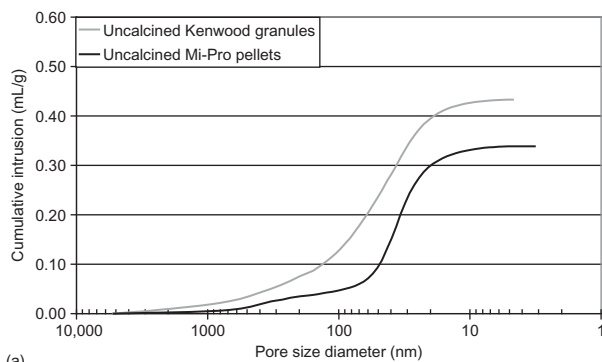
Friability measurements showed that the Mi-Pro process gave pellets three times less friable than Kenwood granules (6.7% versus 20.7%) in agreement with their respective sphericity (Table 1). This lower friability could also be explained by the higher densification involved during high-shear granulation. Visavarungroj and Remon⁶⁴ have also observed that high-shear granulation gave less friable granules than planetary mixer. However, the higher densification might be unfavorable when considering porosity requirements for this

application and should be evaluated by mercury porosity measurements. In the case of Kenwood granules, the initial friability was high, probably due to the low shear involved during the granulation process inducing a low interparticulate cohesion and a lesser binding effect of ST 200. For both Kenwood and Mi-Pro granules, friability increased when the pore former was removed. It was twice as high in the case of Mi-Pro pellets whereas there was only a 3% increase for Kenwood granules. High-shear granulation was responsible for high densification and consequently low friability for Mi-Pro pellets, which greatly increased after the removal of pore former. However, Mi-Pro pellet friability was still 40% lower than that of Kenwood granules. These results were in agreement with the creation of granule porosity and should be confirmed by mercury porosimetry.

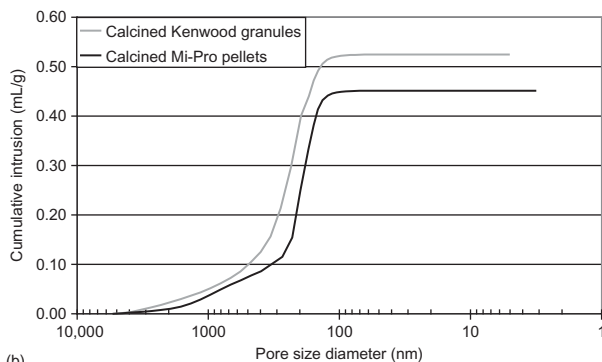
Porosity measurements indicated that both types of granulation processes created porous agglomerates. Porograms displayed pore size diameters varying from 5–150 nm to 150–1000 nm, whatever the granulation process (Table 1 and Figure 2a and b), as previously indicated by Sheskey and Williams⁶³. However, pellet porosity was higher for Kenwood granules (54.4% versus 47.9%) in correlation with their higher specific surface area and lower densification which was supported by friability measurements. Similar observation was made by Sheskey and Williams⁶³. After heating, granule porosity increased about 10%, up to 61.2% and 57.7%, respectively, as suggested by their higher friability. This porosity increase was close to the initial amount of pore former, as shown by the literature^{23,65,66}. Nevertheless, Mi-Pro pellets were less porous than Kenwood granules, which explained their lower friability. Since calcium phosphate granules would further be used as a drug delivery system into bone defects, it was interesting to consider pellet porosity after ibuprofen loading. Porosity measurements indicated that pellet porosity was almost completely filled regardless of the granulation process (Figure 2c). However, as Kenwood granule and Mi-Pro pellet initial porosities were different, dissolution data should be taken into consideration to evaluate drug content and DLE as well as to study the effect of the granulation process on ibuprofen release.

Effect of granulation process on ibuprofen loading and release

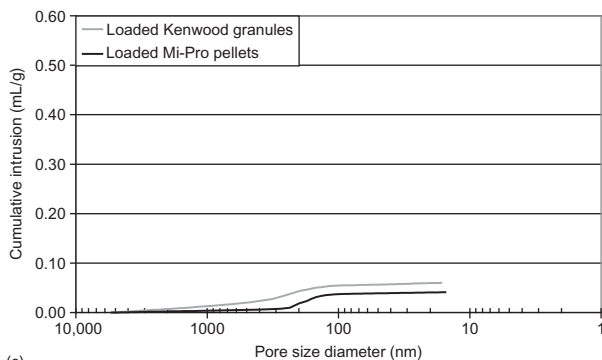
Drug content and DLE (Table 2) indicated that the loading procedure deposited the expected ibuprofen quantity, whatever the granulation process. Furthermore, release profiles of Kenwood and Mi-Pro granules (Figure 3) showed that the entire loaded ibuprofen quantity was released during dissolution test, showing that no irreversible binding occurred between ibuprofen and CaP matrix.



(a)



(b)



(c)

Figure 2. Cumulative porograms of Kenwood granules and Mi-Pro pellets (a) before heat treatment, (b) after calcination, and (c) after ibuprofen loading.

Table 2. Drug contents and drug-loading efficiencies.

	Kenwood	Mi-Pro
DC (%)	36.8 ± 0.2	36.5 ± 0.6
DLE (%)	102.3 ± 0.5	101.5 ± 1.8

Dissolution kinetics showed slower ibuprofen release from Mi-Pro pellets, highlighted by the 24% increase in TW 80% value, compared to Kenwood granules (Table 3). This result could be explained by the slightly higher porosity observed in the case of Kenwood granules. Therefore, as drug contents indicated that the same ibuprofen quantity was loaded, this difference could be attributed to a different drug

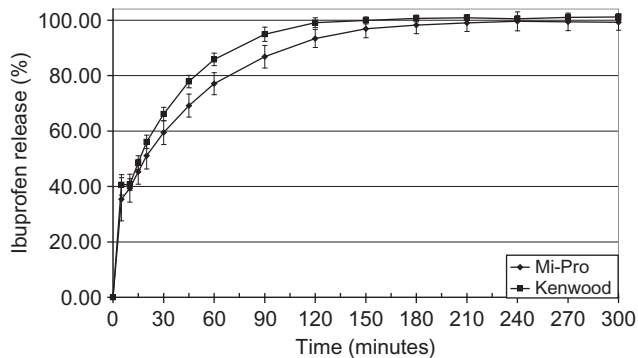


Figure 3. Ibuprofen release kinetics for both types of granule.

Table 3. Modeled dissolution characteristics as a function of the granulation process.

Parameters		Kenwood	Mi-Pro
Weibull	TW 80% (minutes)	53	66
$f1$ difference factor			6.5
$f2$ similarity factor			67.9
Statistical significance		No difference	
Higuchi	R^2 (%)	0.995	0.992
Hixson-Crowell	R^2 (%)	0.995	0.992
Kopcha	R^2 (%)	0.999	0.999
	A/B	5.12	4.01

substance distribution between Mi-Pro pellets and Kenwood granules. It might be assumed that ibuprofen, after the complete filling of the porous volumes, would coat the granule surfaces to a larger extent in the case of Mi-Pro pellets. Ibuprofen inside the pellets would thus be less accessible whereas the dissolution medium could penetrate more easily in the Kenwood granules.

Kenwood and Mi-Pro granule dissolution profiles were compared using difference ($f1$) and similarity ($f2$) factors (Table 3) in order to further evaluate the effect of the granulation process on ibuprofen release. The test indicated that granulation process did not induce statistically different dissolution kinetics of ibuprofen from either granule types, even if the TW 80% was higher for Mi-Pro pellets (Table 3). This result confirmed previous observations⁶² explaining that drug dissolution was not affected by the mixer type but by the formulation.

Finally, dissolution data of Kenwood and Mi-Pro granules were modeled in order to determine the release mechanism (Table 3). The correlation coefficients (r^2) indicated that data did not closely fit to Higuchi or to Hixson-Crowell equations, suggesting that dissolution was not controlled by a unique mechanism. A strong correlation ($r^2 \geq 0.999$) with the Kopcha model, regardless of the granulation process, confirmed the coexistence of diffusion and erosion. Furthermore, the A/B ratio was in both cases greater than 1, indicating that the release mechanism was mainly controlled by diffusion for both processes.

Conclusion

The aim of this work was to study the influence of two granulation processes, low- and high-shear granulations, on physicochemical properties as well as on ibuprofen dissolution from implantable loaded calcium phosphate granules. This study first demonstrated that the two processes resulted in calcium phosphate granule elaboration. However, low-shear granulation led to less spherical and more friable granules than pellets prepared by high-shear granulation. Nevertheless, both types of granules had a similar composition as highlighted by their respective pycnometric densities. Kenwood granules showed a slightly higher specific surface area than Mi-Pro pellets but lower initial packing and higher friability in relation to the low densification involved during the granulation process. Furthermore, the slight increase in Kenwood pellet porosity, highlighted by higher friability, was not statistically different when considering the dissolution profiles of both types of pellets and did not induce a higher DLE. Finally, the granulation process did not affect the ibuprofen release mechanism and diffusion prevailed in both cases.

Therefore, both Kenwood granules and Mi-Pro pellets might be suitable as bone defect fillers and local drug delivery systems, when considering their porosity favorable to drug loading and release as well as to extracellular liquid exchanges. Nevertheless, Mi-Pro pellets would be better candidates as far as they were more spherical, ensuring

- regular deposition of drug substance;
- easy handling and free flowing into bone cavities;
- controlled macroporosity of the implanted material, enabling osteoconduction;

and less friable, which leads to

- a limited deformation during the bone defect filling by the surgeon;
- a satisfying mechanical strength.

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Declaration of interest: The authors report no conflicts of interest.

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