Ibuprofen-loaded calcium phosphate granules: Combination of innovative characterization methods to relate mechanical strength to drug location

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A B S T R A C T

This paper studies the impact of the location of a drug substance on the physicochemical and mechanical properties of two types of calcium phosphate granules loaded with seven different contents of ibuprofen, ranging from 1.75% to 46%. These implantable agglomerates were produced by either low or high shear granulation. Unloaded Mi-Pro pellets presented higher sphericity and mechanical properties, but were slightly less porous than Kenwood granules (57.7% vs 61.2%). Nevertheless, the whole expected quantity of ibuprofen could be integrated into both types of granules. A combination of surface analysis, using near-infrared (NIR) spectroscopy coupling chemical imaging, and pellet porosity, by mercury intrusion measurements, allowed ibuprofen to be located. It was shown that, from 0% to 22% drug content, ibuprofen deposited simultaneously on the granule surface, as evidenced by the increase in surface NIR signal, and inside the pores, as highlighted by the decrease in pore volume. From 22%, porosity was almost filled, and additional drug substance coated the granule surfaces, leading to a large increase in the surface NIR signal. This coating was more regular for Mi-Pro pellets owing to their higher sphericity and greater surface deposition of drug substance. Unit crush tests using a microindenter revealed that ibuprofen loading enhanced the mechanical strength of granules, especially above 22% drug content, which was favorable to further application of the granules as a bone defect filler.

1. Introduction

Hard tissue diseases and defects, osteoporosis and osteoarthritis have led to an extensive need for appropriate implantable materials for bone replacement surgery. Among alternatives to bone grafts, synthetic calcium phosphate based ceramics are widely used [1,2] owing to their chemical composition close to the bone mineral phase, which leads to high bone bonding ability [1,3–5]. Porous bioceramics have been developed to mimic the porous architecture of trabecular bone. The advantage of the porous structure is that it provides appropriate space for bone ingrowth. Indeed, when porosity is large enough (pore size > 100 μm), the implanted material is progressively invaded and substituted by bone tissue [6–9]. Bioceramics can also be drug loaded in order to be used as delivery systems [10–13]. In this case, smaller pores ~10 μm in diameter are intended to confine drug substances inside the ceramic reservoir. By modulating the pore size and connections, adjustment of the release kinetics can be performed [14]. Previous work has shown that microporous calcium phosphate pellets obtained by granulation followed by a calcination step can be loaded with ibuprofen [15–17]. This physical presentation (spherical implants ~900 μm in diameter) allows the filling of complex-shaped bone defects rather than blocks, while keeping regular macroporosity (intergranular spaces ~180 μm) necessary for bone ingrowth. Such spherical granules are also interesting for drug delivery applications, as their controlled surface allows the deposition of regular and reproducible amounts of therapeutic agents. The choice of ibuprofen was directed by the fact that this anti-inflammatory agent, already associated with bone implants (bioactive glass-polymer [18] and hydroxyapatite [19]), could contribute to the local treatment of inflammation [20,21] following surgery or to the treatment of bone loss in periodontitis [22]. Moreover, this drug substance has been used extensively as a model drug in the development of sustained and controlled drug delivery systems [23–26] because of its short biological half-life.

The physicochemical, textural and dissolution properties of these ibuprofen-containing pellets allow them to be considered as drug delivery systems [15–17,27,28]. Nevertheless, complete characterization, including considerations of the mechanics and location of the drug substance, is required to evaluate the end-use properties of the granules.

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The usual functionality tests (packing measurements, flow rate measurements, diametral compression test after granule compaction, friability measurements) characterize the global and averaged properties of large particulate populations. However, unitary tests on individual granules may be useful when only small amounts of products are available, provided they represent the whole sample properties, and to evidence inter-individual variations that may be hidden in the case of global tests.

Concerning the mechanical properties of granules, various tests can be carried out, such as friability measurements, uniaxial compression between two parallel plates, impact against a surface and indentation methods [29–32]. Standard friability measurement is always performed on granule samples; impact against a surface and indentation methods are carried out on individual agglomerates, whereas uniaxial compression can be conducted either on a whole sample or on individual granules. In the latter case, not only average strength is determined, but variations between single agglomerates can also be expressed from the weakest and the strongest values [33]. In this study, the granule mechanical properties were determined using a single-granule crush test carried out with a microindenter and compared with friability measurements.

The development of innovative drug delivery systems in pharmaceutical and biomaterial fields requires the use of new techniques to investigate and control these products. Methods such as spectrometry, chromatography, colorimetry, refractometry, X-ray diffraction, solid nuclear magnetic resonance and mass spectrometry are performed to identify and, for some of these, to assay the drug substances. Other techniques have been developed to characterize the layered structures. However, most of them are unspecific (e.g., weight gain during coating) or destructive (e.g., electron microscopy of cross sections) [34,35] and do not allow precise location of the drug substances. In contrast, Raman and near-infrared (NIR) spectroscopy are rapid and non-destructive methods that require no sample preparation [36,37]. Moreover, they are useful for both rapidly quantifying and locating drug substances. In the present work, NIR spectroscopy coupling chemical imaging (NIR-CI) and image analysis are tested in order to map the drug substance associated with calcium phosphate granules.

Two types of granules, produced by low and high shear granulation, loaded with various ibuprofen contents are compared. This paper aims to study the impact of drug substance location on the physicochemical and mechanical properties of ceramic pellets, by combining several characterization methods.

2. Materials and methods

2.1. Materials

Porous calcium phosphate granules were fabricated by either low shear (Kenwood, model KM201, Kenwood Ltd., UK) or high shear wet granulation (Mi-Pro, Pro-C-epT, Zelzate, Belgium) as described in previous work [15–17]. Calcium phosphate (Batch No. G8138/3, Cooper, France) was granulated with pregelatinized starch (Sepistab ST 200, batch number 80551, Seppic, France) also acting as a pore former after removal by heat treatment. The 710–1000-μm fraction of porous granules was drug loaded with an ethanolic ibuprofen solution by solvent evaporation in a Rotavapor (Büchi, Switzerland). Seven percentages of drug content were tested: 1.75%, 3.5%, 7%, 12.5%, 22%, 36% and 46%.

2.2. Methods

2.2.1. Morphological evaluation

Unloaded and loaded granule morphology was observed by scanning electron microscopy (SEM; Stereoscan S260, Leica, Cambridge, UK) after Au/Pd metallization.

An automated particle imaging system (Morphologi G3, Malvern Instruments, Malvern, UK) was used to measure the size and shape parameters of a large number of granules per batch (more than 200). High sensitivity circularity (HSC) is defined as:

$$\mathrm{HSC} = \mathrm{circularity}^2 = 4\pi \times \frac{\mathrm{area}}{\mathrm{perimeter}^2}$$

HSC is more sensitive than circularity for comparing particles of similar morphology. The HSC of a sphere equals 1.

2.2.2. Specific surface area measurement

The specific surface area (S_{spe}, $m^2\ g^{-1}$) of the unloaded granules was determined by nitrogen adsorption using a Gemini 2360 Analyzer (Micromeritics Instruments Inc., Norcross, GA). Prior to measurements, samples were degassed for three days at room temperature under a 50 mTorr vacuum (VacPrep 061, Micromeritics Instruments Inc., Norcross, GA). The specific surface area was calculated by the BET multipoint equation [38]. The sample weight was adjusted to ensure a surface of at least 1 m^2 in the cell. Measurements were repeated until the value was stabilized.

2.2.3. Density measurements

The pycnometric density (d_{pycno}, $g\ cm^{-3}$) of raw materials and granules before and after loading was determined using an AccuPyc 1330 helium pycnometer (Micromeritics Instruments Inc., Norcross, GA) [39]. The samples were previously degassed under the same conditions as for specific surface area measurements. Measurements were repeated until stabilization.

Theoretical density ($d_{pycno\ theo}$) could be calculated by taking into account the weight fraction of each constituent (α_n) and their respective measured pycnometric density (d_n) according to the following equation:

$$d_{\mathrm{pycno\ theo}} = \frac{1}{[(\alpha_a/d_a) + (\alpha_b/d_b)]} \quad (1)$$

Bulk (d_{bulk}, $g\ cm^{-3}$) and packed (d_{packed}, $g\ cm^{-3}$) densities were determined in triplicate, using a 1 cm^3 cell according to:

$$d_{\mathrm{bulk}} = \frac{m}{V_0} \quad (2)$$

$$d_{\mathrm{packed}} = \frac{m}{V_{0.5}} \quad (3)$$

where m is the mass of the granule sample freely poured into the cell, V_0 is the corresponding volume (1 cm^3) and $V_{0.5}$ is the volume occupied by granules under a uniaxial pressure of 0.5 MPa (Lloyd Instrument LR30K, Fareham, UK). This pressure corresponded to the packing and slippage of the particles without any deformation [40].

2.2.4. Porosity investigation

Porosity measurements were performed using a mercury intrusion porosimeter (Autopore IV 9500, Micromeritics Instruments Inc., Norcross, GA) with a 5 cm^3 powder penetrometer. Mercury intrusion volumes were recorded. The intergranule porosity was not considered here as it was only partially measured owing to mercury porosimetry limitations in the case of large spaces. Only the intragranule porosity (pellet porosity, %) was calculated according to:

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

where V_{solid}, the solid volume of the granules, is deduced from the pycnometric measurements, and V_{intra} is the porous volume of the granules.

2.2.5. Mechanical properties

2.2.5.1. Friability measurement. Friability measurements were performed on 10 g of unloaded granules which were introduced into a glass container [41]. They were subjected to horizontal oscillations (240 oscillations min^{-1} for 240 s) in an oscillating apparatus (Friabimat, GTA-120, Erweka, Heusenstamm, Germany). After sieving through a 710 μm sieve to remove fine particles, granules were weighed, and the friability (F, %) was calculated according to the following equation:

$$F = \frac{m_1 - m_2}{m_1} \times 100 \quad (5)$$

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. The test was performed in triplicate.

2.2.5.2. Granule crush test. A unit crush test was performed on the granules before and after ibuprofen loading by instrumented indentation using a Micro Hardness Tester (MHT, CSM Instruments, Peseux, Switzerland). A stainless steel punch 2 mm in diameter, normal to the pellet surface, was linearly driven into the granule by applying an increasing load up to the breaking of the granule. The maximal load of the sensor was 30 N, and the load resolution was 0.3 mN. The test was performed on about 10 granules. The contact force detection between the steel punch and the granule was 10 mN.

2.2.6. NIR chemical imaging

Ibuprofen location on calcium phosphate granules was studied using a NIR-CI system [42–44]. SyNIRgi apparatus (Malvern Instruments, Malvern, UK) equipped with a focal plane array detector (320 × 256 pixels) was used in this work. Spectra were collected from 1200 to 2400 nm in 10 nm increments and 16 co-additions. Two magnifications were used for this work: the field of view was set to 12.8 × 10.2 mm, providing a pixel magnification of 40 μm for parallel imaging of multiple granules, while a magnification of 8.1 μm per pixel was used to investigate individual granules. All data were acquired in diffuse reflectance, a process by which the source radiation interacts with the surface of the sample, and the radiation diffusely reflected in the direction of the camera is measured. Dark and bright background image cubes were acquired at initiation, followed by successive sample cubes. For each sample scanned, 81,920 spectra were collected in ~2 min to form a so-called data cube, in which the x- and y-axes correspond to the physical location of the pixel, and the z-axis contains the spectral data.

All data were analyzed with ISys 5.0 Data Analysis Software (Malvern Instruments, Malvern, UK). Sample data were converted to absorbance (A) according to the following equation:

$$A = \log 1/R \quad (6)$$

where R was the reflectance obtained by processing the sample (S), dark (D) and background (B) image cubes as follows:

$$R = \frac{S - D}{B - D} \quad (7)$$

At the same time, a spectral reference library was created by collecting images of pure ibuprofen and calcium phosphate granules.

NIR-CI benefits from the chemical specificity of NIR spectroscopy and the spatial resolution of a two-dimensional camera image. In this particular case, the distribution of ibuprofen will be mapped on calcium phosphate granules provided their respective NIR spectra do not overlap. It was possible to investigate the chemical composition of a few granules at high magnification to gain an understanding of the spatial location of the components. A low magnification can also be selected to image a large number of granules for comparison of overall surface drug load or to investigate the distribution of components inside the cross sections of granules.

3. Results and discussion

3.1. Influence of granulation on granule properties

Table 1 summarizes the physicochemical characteristics of the granules before drug loading. The granules are called Kenwood granules when obtained with Kenwood equipment and Mi-Pro granules when produced with Mi-Pro.

Pycnometric densities of Kenwood and Mi-Pro granules were similar before loading, confirming that the heat treatment, removing the pore former, led to a similar CaP matrix whatever the granulation process.

In contrast, the bulk density distinguished the two types of granules: Mi-Pro high shear conferred a higher bulk density to the pellet bed (0.71 g cm^{-3} vs 0.55 g cm^{-3}). As the specific surface area and particle size distribution of Kenwood and Mi-Pro granules were relatively similar, the bulk density difference might be attributed to their respective morphology (microscopic observations and circularity coefficient) and porosity, both responsible for closer initial packing of Mi-Pro pellets. For this reason, Mi-Pro pellets would be better candidates for bone defect filling, even though packed densities showed that the same compacity (0.78–0.79 g cm^{-3}) might be reached at low pressure (0.5 MPa) for both types of granules. In fact, as both bulk and packed densities of Mi-Pro pellets were close, pellets would more easily rearrange into the bone defect under the pressure applied by the surgeon to fill the cavity completely.

Moreover, Mi-Pro pellet friability was lower than that of the Kenwood granule: 12.1% and 21.3%, respectively. This value was in accordance with the lower porosity and the more spherical shape previously observed. As this test considered granules rolling and impacting on each other, the friability resulted from both the surface state attrition ability and the intrinsic mechanical strength of the granules. Consequently, it can be assumed that the particles constituting the Mi-Pro pellets presented higher cohesion due to the high densification involved during the granulation process. Granule crush test confirmed this assumption, as the individual strength of Mi-Pro pellets was more than twice as high as the Kenwood granule one (respectively, 750 ± 225 mN and 298 ± 97 mN). Hereafter, only this mechanical test will be performed to characterize the loaded granules, as it required fewer granules than friability measurements did.

3.2. Ibuprofen loading effect on granule properties

For both Kenwood and Mi-Pro granules, pycnometric density values varied as a function of ibuprofen content (Table 2) and were strictly in accordance with theoretical values calculated from respective pycnometric densities of CaP (3.04 g cm^{-3}) and ibuprofen (1.11 g cm^{-3}) (Fig. 1). Consequently, pycnometric density measurements could be proposed as a method for estimating ibuprofen content in the concentration range considered in this study.

Non-loaded Kenwood granules were less circular than Mi-Pro pellets, and circularity determined by Morphologi G3 remained unchanged after the loading procedure (Table 2). These results are in agreement with the SEM images (Fig. 2). It should be noted that the circularity value of granules loaded with 46% ibuprofen was decreased, especially in the case of Mi-Pro pellets, probably due to the formation of an irregular ibuprofen coating outside the granules.

Table 1
Physicochemical properties of non-loaded calcined granules.

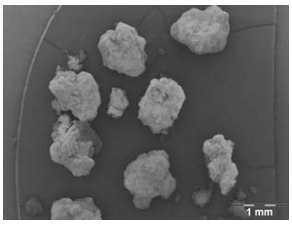
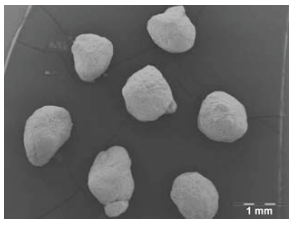
Properties	Kenwood	Mi-Pro
Morphology		
Circularity coefficient	0.76	0.83
d_{pycno} (g cm^{-3})	3.04	3.04
d_{bulk} (g cm^{-3})	0.55	0.71
d_{packed} (g cm^{-3})	0.79	0.78
S_{spe} (m^2 g^{-1})	5.91	5.69
Pellet porosity (%)	61.2	57.7
Friability (%)	21.3	12.1
Rupture strength (mN)	298 ± 97	750 ± 225

Table 2
Loaded granules physicochemical properties.

Ibuprofen content (%)	Kenwood		Mi-Pro	
	d_{pycno} (g cm^{-3})	Circularity	d_{pycno} (g cm^{-3})	Circularity
0	3.04	0.69 ± 0.09	3.04	0.81 ± 0.07
1.75	2.84	ND	2.95	ND
3.5	2.87	0.71 ± 0.07	2.89	0.80 ± 0.07
7	2.73	0.68 ± 0.09	2.71	0.78 ± 0.08
12.5	2.50	0.71 ± 0.07	2.50	0.79 ± 0.08
22	2.18	0.72 ± 0.07	2.17	0.78 ± 0.08
36	1.85	0.72 ± 0.08	1.86	0.77 ± 0.10
46	ND	0.68 ± 0.11	ND	0.74 ± 0.09

ND, not determined.

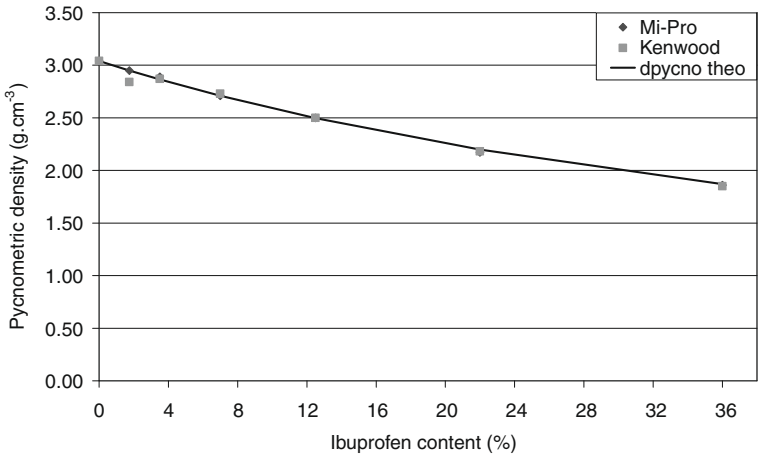


Fig. 1. Evolution of pycnometric density as a function of ibuprofen content.

Fig. 3 presents the rupture strength as a function of the drug content. Results showed that ibuprofen loading increased the mechanical strength of the two types of granules. Moreover, for all ibuprofen contents, Mi-Pro pellets presented a higher cohesion than Kenwood granules: up to 22% ibuprofen content, they were twice as resistant. Beyond this drug content, the slope of the curve was more important, indicating a significant increase in strength with content of drug substance. In this second zone, the evolution was quite similar for the two types of granules, and Mi-Pro pellets remained more resistant whatever the drug content. Results obtained for 46% ibuprofen content should be considered carefully, as granules tended to stick and thus presented an irregular and agglomerated shape. Two hypotheses regarding the location of ibuprofen deposited might be proposed to explain the two regions highlighted on the rupture strength curve: (i) pores could be progressively filled up to a threshold for which the whole porous volume would be completely saturated, and the additional ibuprofen could only be deposited onto granules; (ii) the granule surface

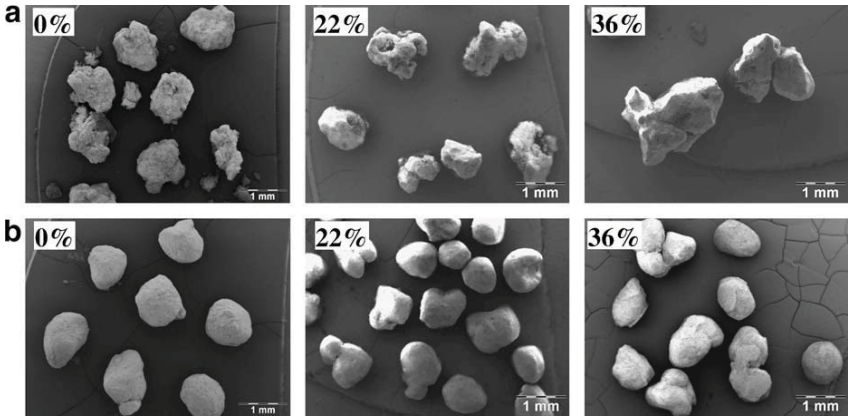


Fig. 2. SEM observations of loaded (a) Kenwood granules and (b) Mi-Pro pellets.

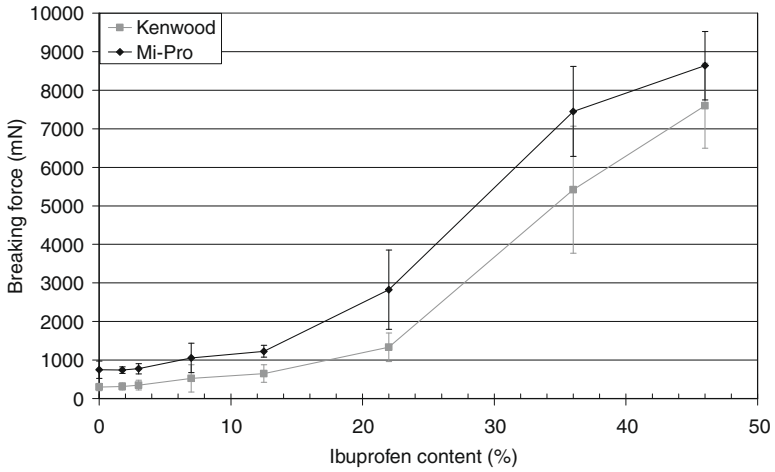


Fig. 3. Evolution of the rupture strength as a function of the ibuprofen content.

could first be coated with the drug substance, and pores would be progressively filled with the increase in quantity deposited.

In both cases, the second step would explain the significant consolidation of the granules.

NIR-CI was performed in order to investigate the location of ibuprofen and to try to determine the sequence of drug deposition. Spectral analyses of the raw materials confirmed that calcium phosphate does not absorb NIR radiation. Ibuprofen presents a complex spectrum with a number of specific absorption bands, such as a sharp band seen in the region 2110–2210 nm (Fig. 4). Consequently, it was possible to integrate the area under the curve (AUC) in this region, which was indicative of the quantity of ibuprofen deposited on granule surfaces for the various ibuprofen contents and the two types of pellets. AUC values increased with the increase in drug content (Fig. 5) and were similar for the two granulation processes up to 22%. Beyond this drug content, AUC strongly increased for both types of granules, but the values were higher in the case of Mi-Pro pellets. However, pycnometric density measurements showed that granules were loaded with the same ibuprofen quantity. One hypothesis to explain this difference was related to the location of ibuprofen. In accordance with their higher sphericity, Mi-Pro pellets may be more regularly coated, whereas the irregular shape of Kenwood granules would induce areas of preferential accumulation of ibuprofen. Another hypothesis would be the more important intrusion of ibuprofen into the pores of Kenwood granules, correlated to their higher porosity, leading to a lower surface content, as measured in the NIR spectra. From 36% up to 46% of drug content, the variation in the AUC value was not significant, indicating that a similar thickness of ibuprofen was measured on the granule surfaces. However, it should be noticed that, as for the granule crush test results, the AUC value determined for granules loaded with 46% ibuprofen should be considered only as a tendency, owing to the propensity of the granules to adhere to each other. NIR-CI performed on granule cross section (Fig. 6) highlighted the presence of ibuprofen inside and outside both types of granules, and confirmed the more regular coating in the case of Mi-Pro pellets, as previously assumed.

The increase in AUC values over all the drug contents, and especially over 22%, suggesting an ibuprofen coating, could explain the strengthening of the granule. The higher breaking force of Mi-Pro pellets previously reported could be maintained by the more regular ibuprofen deposition onto these spheroids. Morphological analysis showed a slight increase in the circularity value with ibuprofen content for Kenwood granules, owing to the initial relatively irregular shape. In contrast, circularity values, relatively high for unloaded Mi-Pro pellets, decreased slightly with ibuprofen deposition. However, these variations were not sufficient to distinguish clearly between the two types of loaded granules and justified further mercury porosimetry investigation to gather information on the pore filling.

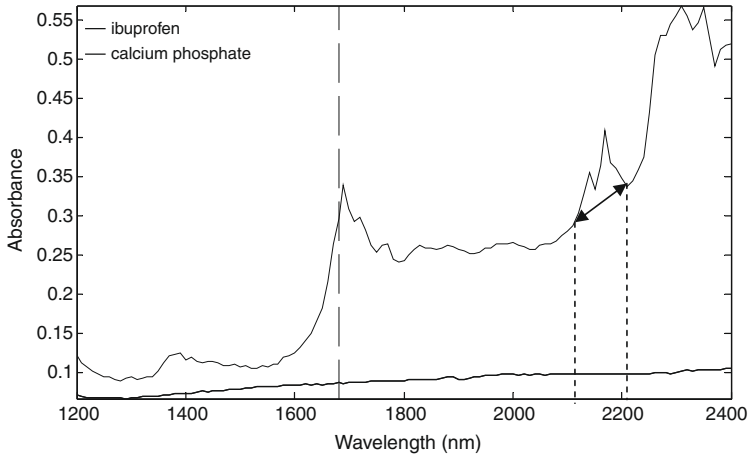


Fig. 4. NIR spectrum of granule constituents.

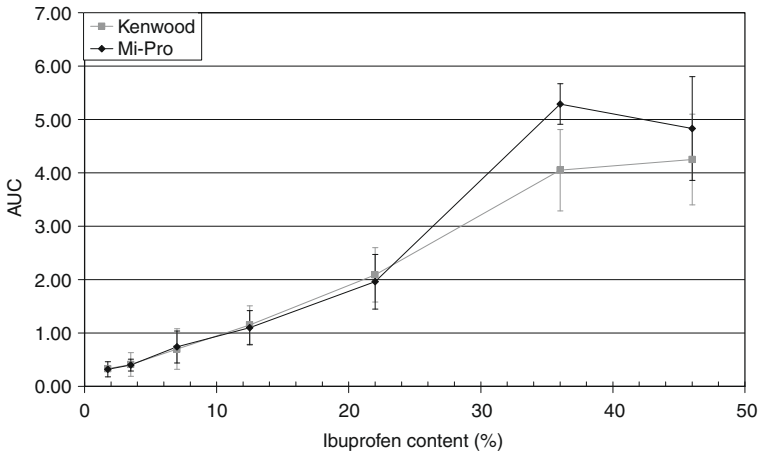


Fig. 5. AUC of ibuprofen loaded pellets in the spectral range 2110–2210 nm.

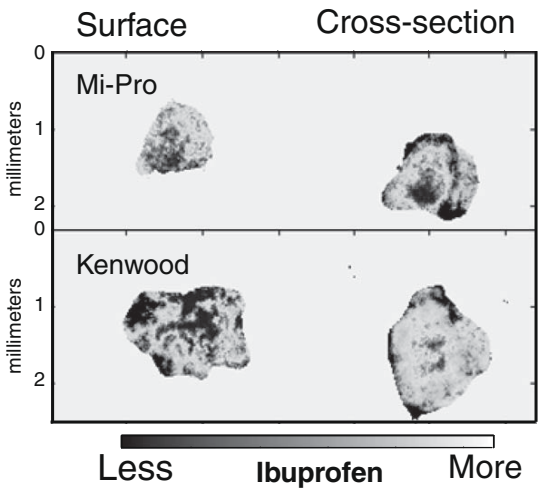


Fig. 6. Ibuprofen location (drug content 46%).

Mercury cumulative porograms are given for drug contents from 0 to 36% (Fig. 7). They show the presence of a main pore range ~3–400 nm for Kenwood granules and 3–300 nm for Mi-Pro pellets, and a second intrusion range corresponding roughly to pore size diameters between 400 and 10,000 nm for Kenwood granules and 300–10,000 nm for Mi-Pro pellets. Thereafter, the main pore range was called "small pores" and the second "large pores". The evolution of the volume of these two pore ranges as a function of the ibuprofen content is shown on Fig. 8. The higher pellet porosity of unloaded Kenwood granules, as previously noted (see Section 3.1), resulted from the higher proportion of "small pores". Indeed, at 0% ibuprofen content, the porous volume of "small pores" equaled 0.43 mL g^{-1} for Kenwood granules, whereas it was 0.34 mL g^{-1} for Mi-Pro pellets. "Large pores" volumes were similar for the two types of granules. The decrease in the porous volume from the first drug contents highlighted, as shown by the NIR spectroscopy (Fig. 5), that ibuprofen deposition occurred not only on the surface, but also into granule pores, regardless of the granulation process. Fig. 8 also indicates that, for 36% ibuprofen, both porosities were totally filled for both types of granules. Moreover, drug loading with increasing ibuprofen contents induced a linear decrease in the "large pore" volumes of both types of granules. For Kenwood granules, "small pore" volumes decreased linearly over all the ibuprofen content range studied, whereas the evolution of Mi-Pro pellet volume presented two stages. From 0% to 22%, the pore volume decreased in the same manner as for

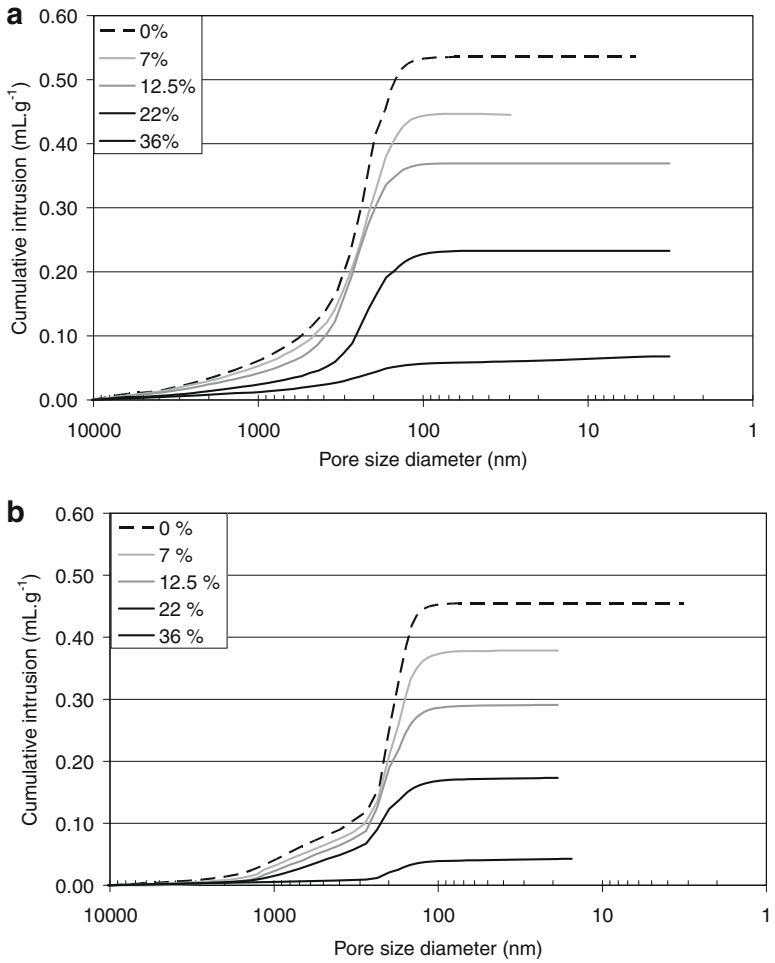


Fig. 7. Cumulative porograms of (a) Kenwood and (b) Mi-Pro granules, as a function of ibuprofen content.

Kenwood granules; above 22%, the available pore volume was lower, and the slope of the evolution was reduced. Comparison of Figs. 5 and 8 indicates that, when most of pellet porosity (<0.20 mL g^{-1}) was filled, additional ibuprofen deposited onto granule surfaces. As both types of granules were loaded with the same amount of ibuprofen, the quantity of ibuprofen deposited onto Kenwood granules was lower than that for Mi-Pro pellets, owing to their higher initial pellet porosity. Therefore, the higher ibuprofen coating on "fully filled" granules induced the high increase in mechanical strength, especially in the case of Mi-Pro pellets (Fig. 3).

4. Conclusion

The aim of this work was to study the impact of the location of drug substance on the physicochemical and mechanical properties of calcium phosphate pellets. Granules produced by two granulation processes and loaded with seven ibuprofen contents were compared.

Unloaded granule characteristic study demonstrated higher sphericity and mechanical strength (evaluated by friability and rupture strength) of Mi-Pro pellets. A bimodal pore size distribution was observed for both types of granules, but Kenwood granules presented a slightly higher total porous volume, explaining their lower rupture strength.

Various characterization techniques were combined to investigate ibuprofen-loaded granules and to try to relate the evolution of their physico-technological properties to drug substance content and location. Thus, it was shown that the whole ibuprofen quantity could be loaded onto both types of granules. Moreover, the drug content could be estimated from pycnometric density measurements. The cross-analysis of surface composition and pore volumes as a function of the drug content highlighted that, from the first drug contents, ibuprofen deposited simultaneously on the surface and inside the pores. From 22% of drug substance, pore filling was almost completed, and additional ibuprofen coated the granule surfaces. As revealed by the unit crush tests, the loading enhanced granule mechanical strength, especially beyond 22%. This strengthening is favorable to further implantation into bone defect cavities, as porous bioceramic applications are often limited by the low resistance of the products. Nevertheless, these initial characteristics might evolve in an osseous environment and should be considered in conjunction with bone colonization kinetics.

In correlation with their further application in bone implant and drug delivery systems, the bioactivity of these loaded pellets must be evaluated in comparison with unfilled granules, as the presence of ibuprofen on the bioceramics could modify blood liquid exchanges, cell adhesion and consequently osteoconduction, and the *in vivo* drug release kinetics must be determined.

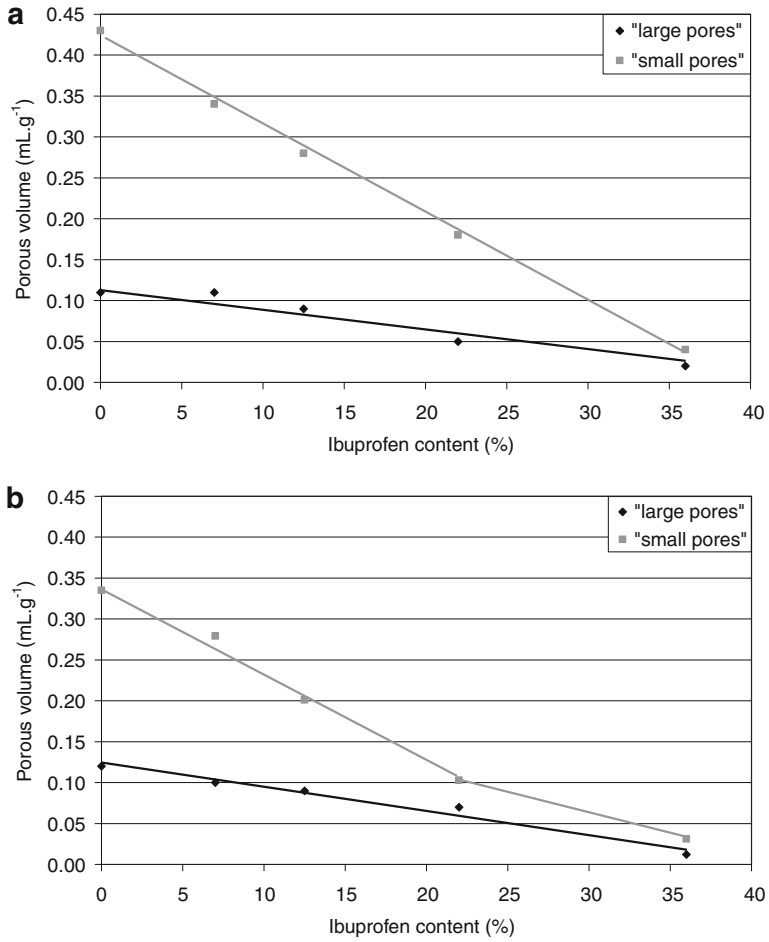


Fig. 8. Evolution of the porous volume of the two pore size diameter ranges as a function of the ibuprofen content for (a) Kenwood granules and (b) Mi-Pro pellets.

Finally, an alternative loading method using supercritical fluids is under investigation in order to avoid the use of solvent, which prevents the transposition of the present fabrication technique on an industrial scale.

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