# Influence of $\alpha$-$Al_2O_3$ morphology and particle size on drug release from ceramic/polymer composites

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In order to test the influence of ceramic morphology and particle size on the behaviour of the ceramic/polymer/drug composite $\alpha$-$Al_2O_3$/poly(L-lactic acid)/poly(methyl methacrylate)/ibuprofen ($\alpha$-$Al_2O_3$/PLLA/PMMA/IB) containing the antiinflammatory drug ibuprofen, have been studied. We have used $\alpha$-alumina synthesised by two preparation methods which provide different morphologies and particle sizes. The influence of these parameters on the ibuprofen release process after the immersion of composites in a buffered solution at pH = 7.4 at 37 °C was analysed. The results obtained show that drug release is facilitated in the samples which have smaller particle size, with spherical morphology and a homogeneous size distribution of $\alpha$-alumina.

It is well known that the morphology and size of particles that constitute a material influence its properties and therefore its applications. In this sense, the behaviour of ceramic/polymer composites could be very different depending on the size and shape of the ceramic particles. This fact may be a worthwhile strategy to achieve a significant improvement on the design and applications of very versatile systems able to act not only as filling elements but also as real drug dosage systems.[1–3]

In an earlier study,[4] composites made by $\alpha$-alumina, together with poly(L-lactic acid), PLLA,[5,6] poly(methyl methacrylate), PMMA,[7,8] and the antiinflammatory drug, ibuprofen,[9] have been synthesised and the drug release process was analysed. $\alpha$-Alumina, the first clinically used bioceramic, was chosen due to its high bioinert character, excellent corrosion characteristics and high wear resistance and strength.[10,11]

Considering the different behaviour of a material depending on the ceramic characteristics, the objective of the present work is to study the influence of the particle morphology and the size of the alumina on the drug liberation from the composites. According to this, different composites containing alumina synthesised by two different methods have been studied.

## Experimental

### Starting materials

The ceramic component, $\alpha$-$Al_2O_3$, was synthesised by two different procedures.

**$\alpha$-$Al_2O_3$n.** This was prepared by nitrate decomposition from $Al(NO_3)_3 \cdot 9H_2O$ through a multistep thermal treatment, firstly at 400 °C for 12 h, 900 °C for 24 h and finally at 1250 °C for 33 h. The reaction product was characterised by X-ray diffraction (XRD) on a Philips X'Pert MPD diffractometer (Cu-K$\alpha$ radiation). All reflections on the XRD pattern could be indexed on the basis of an $\alpha$-$Al_2O_3$ phase[12] and no extra peaks were observed.

The morphology of the ceramic obtained was analysed by scanning electron microscopy (SEM) using a JEOL JSM 6400 microscope. The micrograph [Fig. 1(a)] shows that the powder so obtained is formed by agglomerated particles with irregular morphology and highly heterogeneous size distribution (0.1–10 μm).

**$\alpha$-$Al_2O_3$p.** This was obtained by the pyrosol method.[13] This method involves atomising a liquid solution by an ultrasonic generator into very small droplets (aerosol). The aerosol is conveyed by a carrier gas to the tubular furnace in which the solvent evaporates and the precursor reacts to form a homogeneous powder which is collected by an electrostatic filter. Different parameters must be controlled in order to obtain a powder with desired characteristics. According to a previous study[14] the following conditions were used: a 0.1 M aqueous solution of $Al(NO_3)_3 \cdot 9H_2O$, air as carrier gas (4.5 l $min^{-1}$)

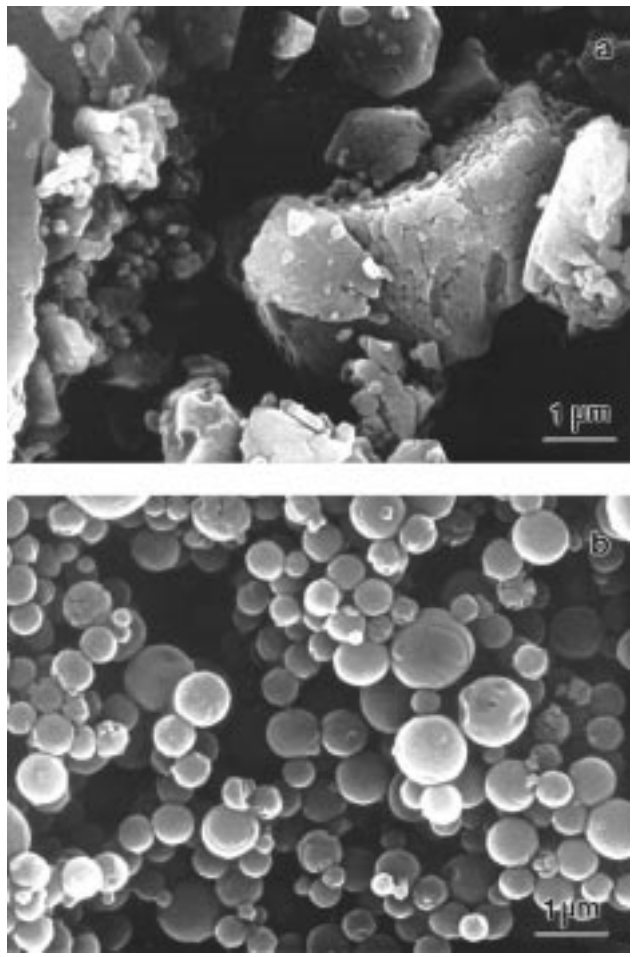


**Fig. 1** Scanning electron micrographs of $\alpha$-$Al_2O_3$ obtained by (a) nitrate decomposition ($\alpha$-$Al_2O_3$n) and (b) the pyrosol method ($\alpha$-$Al_2O_3$p)

and a furnace temperature of 400 °C. The XRD pattern of sample so obtained is characteristic of an amorphous material. Subsequent thermal treatment of this sample at 1250 °C for 5 min, leads to well crystallised α-$Al_2O_3$.

The SEM study of this sample [Fig. 1(b)] shows that it is formed of filled spherical particles showing average diameters ranging from 0.1 to 2 μm.

Therefore, the two preparation methods lead to materials with the same composition, $Al_2O_3$, and corundum type structure, but with very different microstructures. Both the morphology and particle size and size distribution differ substantially enabling a study of the influence of these factors in the drug release from ceramic/polymer composites synthesised with these ceramics.

The continuous phase of the composite system is formed by a mixture of poly(L-lactic acid), and poly(methyl methacrylate). PLLA was prepared by the polycondensation of L-lactic acid in a solution of xylene at 130 °C, using toluene-*p*-sulfonic and boric acids as catalysts. The average molecular mass was determined by SEC (size exclusion chromatography) giving a value of $M_n = 3600$. The XRD pattern of this polymer is shown in Fig. 2. DSC measurements were carried out in a Seiko SSI SSC/5200 instrument at a heating rate of 10 °C $min^{-1}$ between 30 and 200 °C, and the corresponding DSC curve is displayed in Fig. 3. An endothermic process is observed between 90 and 140 °C with a minimum at 135 °C, which corresponds to the melting point of the crystalline fraction of PLLA. This behaviour is characteristic of polymeric materials which coexist in an amorphous matrix with crystalline domains.[15]

PMMA was obtained by free-radical polymerisation of the methyl methacrylate monomer, MMA, used as received without purification, initiated by benzoyl peroxide at 60 °C.

The drug charged into the composites was ibuprofen [IB 2-(4′-isobutylphenyl)propanoic acid] which is an analgesic/antiinflammatory agent. This compound is a derivative of propionic acid with low toxicity.

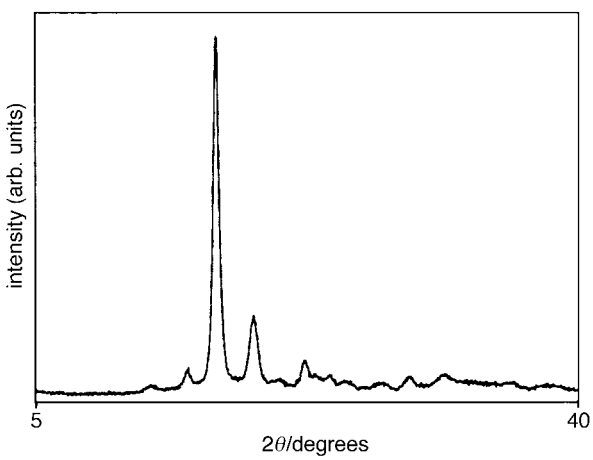


**Fig. 2** XRD pattern of PLLA

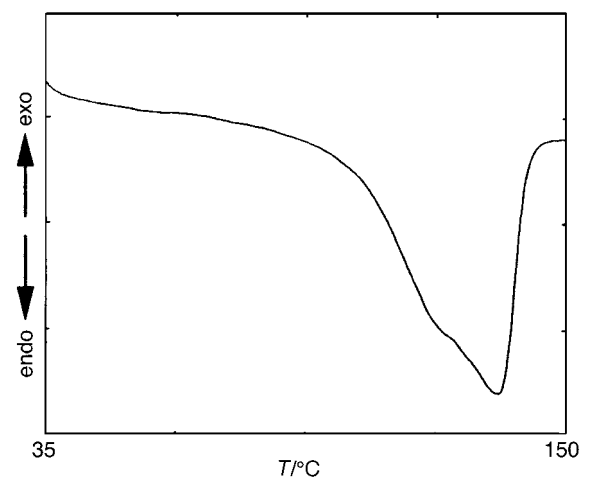


**Fig. 3** DSC curve of PLLA

### Composites

Ceramic/polymer composites were prepared by the free radical polymerisation of a mixture of α-$Al_2O_3$, PLLA, IB and MMA using 0.5 mass% of benzoyl peroxide as initiator. Cylindrical specimens (6 mm diameter, 10 mm length) were obtained using Teflon moulds at a polymerisation temperature of 60 °C over 24 h. A previous study on this system[4] showed that to obtain a significant liberation of ibuprofen, the presence of both α-$Al_2O_3$ and PLLA was required; in the absence of PLLA or $Al_2O_3$ no significant release of IB was observed after 25 days of testing. In order to study the influence of the ceramic characteristics on the delivery process, four series of experiments were prepared (Table 1). Series A and C were with all the components, *i.e.* α-$Al_2O_3$, PLLA, PMMA and IB, whereas series B and D were prepared without the biodegradable polymer PLLA. The difference between series A/C and B/D is that series A and B contain alumina obtained by nitrate decomposition (α-$Al_2O_3$n) whereas series C and D contain alumina prepared by the pyrosol method (α-$Al_2O_3$p). In all series, two samples with different IB content were synthesised.

The prepared composites were characterised by thermogravimetric analysis (TGA), $^1$H NMR, X-ray diffraction (XRD) and differential scanning calorimetry (DSC).

TGA was carried out on a TG-DTA 320 Seiko thermobalance with a heating rate of 10 °C $min^{-1}$ in the range 30–500 °C.

$^1$H NMR spectra were obtained using a Varian XL300 instrument after extraction of the organic components from the composite specimens overnight in hot chloroform. The solvent was evaporated at low pressure and the dry residue analysed in a solution of $CDCl_3$ (5 m/v %) at 40 °C, using tetramethylsilane as an internal standard reference.

X-Ray data were obtained, using Cu-Kα radiation, on a Philips X'Pert MPD diffractometer equipped with a multipurpose sample holder for non-destructive analysis of samples which allows a study of the crystallinity of the components present in the cylinder.

DSC measurements were carried out using a Seiko SSI SSC/5200 instrument at a heating rate of 10 °C $min^{-1}$ in the range 25–200 °C.

### *In vitro* release

The release of ibuprofen from the cylindrical composites was followed after the immersion of the cylinders in 20 ml buffered solution of phosphate ($KH_2PO_4$–$K_2HPO_4$) at pH = 7.4 and 37 °C. The concentration of free ibuprofen in the solution was followed by UV spectroscopy measuring the absorption at $\lambda_{max} = 264$ nm, using a Perkin-Elmer 554 spectrophotometer. Previously, a calibration curve with pure ibuprofen was obtained.

## Results and Discussion

Hard cylindrical ceramic/polymer composites were obtained by free radical polymerisation as described in the Experimental section.

The composition of the samples prepared was determined by two complementary characterisation techniques, TGA and $^1$H NMR spectroscopy. The content of α-$Al_2O_3$ was calculated from TGA by comparing the mass% loss assigned to the thermal degradation of the organic components, with the mass% of the residue at 500 °C (identified as α-$Al_2O_3$) which gives the average composition of the ceramic in the specimen

**Table 1** Composition of prepared composites. Series A and B are prepared with $\alpha$-$Al_2O_3$n and series C and D with $\alpha$-$Al_2O_3$p

| series | mass% PLLA experimental[a] (theoretical) | mass% PMMA experimental[a] (theoretical) | mass% IB experimental[b] (theoretical) | mass% $\alpha$-$Al_2O_3$ experimental[b] (theoretical) |
|---|---|---|---|---|
| A | 28 | 28 | 11 | 33 |
| | (32) | (32) | (9) | (27) |
| | 24 | 24 | 25 | 27 |
| | (29) | (29) | (17) | (25) |
| B | — | 57 | 12 | 31 |
| | | (64) | (9) | (27) |
| | — | 51 | 23 | 26 |
| | | (58) | (17) | (25) |
| C | 29 | 32 | 12 | 27 |
| | (32) | (32) | (9) | (27) |
| | 28 | 27 | 20 | 25 |
| | (29) | (29) | (17) | (25) |
| D | — | 60 | 11 | 29 |
| | | (64) | (9) | (27) |
| | — | 52 | 22 | 26 |
| | | (58) | (17) | (25) |

[a]Determined by $^1$H NMR spectroscopy. [b]Determined by TGA.

analysed. In order to determine the homogeneity of distribution of the ceramic component in the composite, each cylinder was cut into four equal pieces, and the $\alpha$-$Al_2O_3$ content was analysed in each by thermogravimetric analysis. The differences in composition between pieces of the same sample were always $<2$ mass%. The average data obtained are collected in the fifth column of Table 1.

It is possible to determine the average content of the organic components, PLLA, PMMA and IB, by analysis of the $^1$H NMR spectra of the whole organic fractions isolated. The selected signals for this analysis were: $\delta$ 7.3–7.1, which corresponds to the aromatic protons of IB, the signal centred at $\delta$ 5.20 assigned to the CH group of lactic acid units along the polymeric chains, and the signal at $\delta$ 3.55 which corresponds to the methoxy $CH_3O-$ group of the MMA units. Comparison of the integrated intensities of these signals provides the average molar composition of the three components with an accuracy of $\pm 2$%. The mass% of these components was calculated by taking into consideration the % alumina obtained by TGA and results are collected in Table 1.

Characterisation of the composites by XRD allows identification of the crystalline components. Fig. 4 shows the XRD patterns corresponding to series B, C and D with the highest content of IB (the XRD patterns of series A are similar to those obtained for series C). In the XRD patterns of series A and C, diffraction maxima assigned to $\alpha$-$Al_2O_3$, PLLA and ibuprofen[16] can be observed. On the other hand, in samples prepared without PLLA (series B and D), reflections corresponding to $\alpha$-$Al_2O_3$ (series B) or $\alpha$-$Al_2O_3$ and IB (series D) are observed. This means that IB is in a crystalline form either when PLLA and $\alpha$-$Al_2O_3$ are present, or PLLA is absent but $\alpha$-$Al_2O_3$p is used for the preparation of composites.

These results are supported by the analysis of composites by DSC. Fig. 5 shows the DSC curves for series B, C and D, for samples prepared with 17 mass% of IB. The DSC diagrams of composites of series A and C (with all the components) show two endothermic process centred around 60 and 115 °C. These peaks can be assigned to the melting of IB and crystalline fraction of PLLA, respectively. On the other hand, if we compare the DSC curves corresponding to the composites prepared without PLLA (series B and D), the melting process of IB is only observed in series synthesised with $\alpha$-$Al_2O_3$p (series D).

Therefore, the results obtained by both XRD and DSC techniques confirm that in the series with $\alpha$-$Al_2O_3$, PLLA and PMMA (series A and C), the IB is in a crystalline form, whereas in series without PLLA, amorphous (series B) or crystalline IB (series D) is found. It is necessary to realise that during the synthesis of the composites the melting point of IB is exceeded and once it melts, if the conditions are not suitable, it does not crystallise again. This means that, as previously observed,[4] during the preparation of the composites, the presence of $\alpha$-$Al_2O_3$ together with PLLA favours crystallisation of IB. However, it is possible to have crystalline IB in the composites without PLLA, if $\alpha$-$Al_2O_3$ prepared by the pyrosol method is used. In this sense, the $\alpha$-$Al_2O_3$ particles, with spherical morphology and small size, could act as crystallisation sites, given suitable conditions for nucleation and crystal growth of ibuprofen. These conditions do not seem to be realised in the presence of $\alpha$-$Al_2O_3$n, constituted by agglomerated particles with irregular morphology and heterogeneous size distribution. Considering this, and in order to elucidate if the size of the ceramic particle is a significant determining factor, mechanochemical treatment of $\alpha$-$Al_2O_3$n to obtain similar particle sizes to those found in $\alpha$-$Al_2O_3$p pyrosol, is in progress.

The different characteristics observed in the series are reflected in the release of ibuprofen from these composites. Fig. 6 shows the cumulative release of IB for the four series prepared with the highest content of the drug. Data obtained from series without alumina are also depicted. It can be observed that the IB release is lower in series prepared without PLLA (B and D) or without alumina with respect to series with both components.

On the other hand, the IB release is very similar in those series with $\alpha$-alumina and PLLA (series A and C). These series present a relatively fast initial period releasing approximately a 30 mol% of IB in 15 h, followed by a controlled release of the drug to practically 100 mol% of charged IB after 25 days of immersion. This behaviour is related, on one hand, with the crystallinity of IB (due to the presence of $\alpha$-$Al_2O_3$ together with PLLA), on the other with the biodegradable character of PLLA that favours the release.[4]

In series prepared without PLLA two different types of behaviour are observed. In composites of series B, synthesised with $\alpha$-$Al_2O_3$n, a low IB release level is observed (18 mol% in 25 days), whereas in series D, with $\alpha$-$Al_2O_3$p, 80 mol% of charged IB is released after the same immersion time. This value is slightly lower that those observed in series A and C, due to the absence of biodegradable polymer PLLA. The differences observed in the two series without PLLA can be explained by the crystallinity of the drug in both series. The amorphous state of IB in series B favours interactions of the drug with the carboxylic ester groups of PMMA, increasing

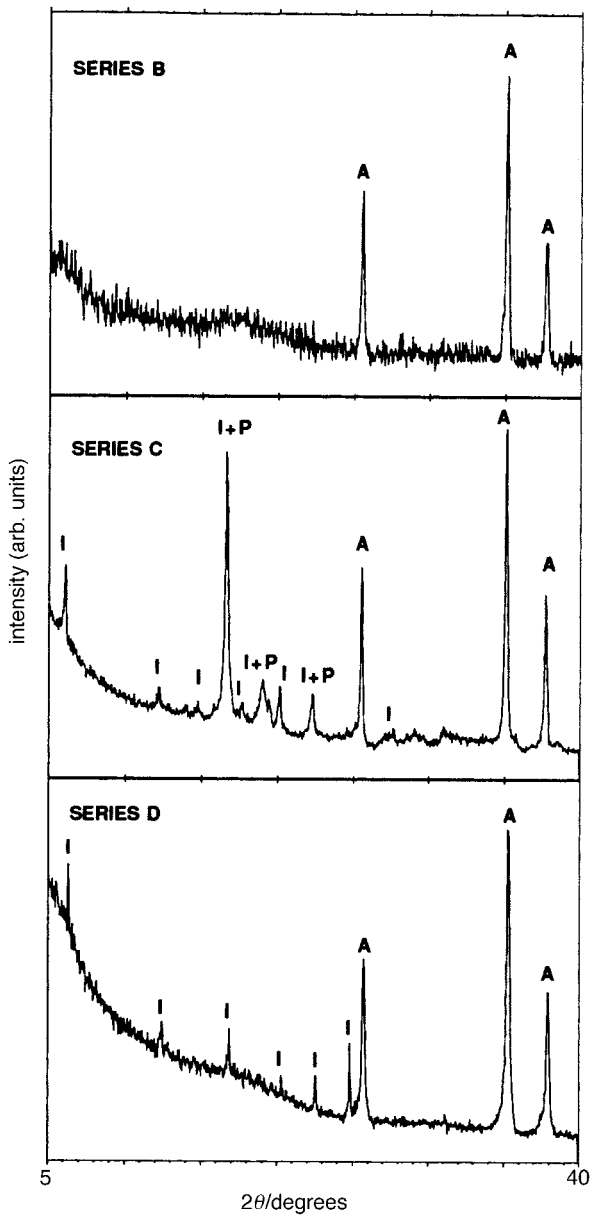


**Fig. 4** XRD patterns of composites of series B, C and D with 17 mass% IB (XRD pattern of series A is similar to that obtained for series C). A = α-$Al_2O_3$; I = ibuprofen; P = poly(L-lactic acid).

the hydrophobic character of the system which will cause low delivery levels to aqueous solution.

According to our experimental data, an appreciable release of drug from the composites is obtained when the ibuprofen is in a crystalline form which is favoured by the presence of α-alumina together with PLLA. However, it is possible to facilitate the crystallisation of IB in the absence of PLLA only if we use α-alumina obtained by the pyrosol method, which produces particles with favourable characteristics, *i.e.*, spherical shape, small size and homogeneous size distribution.

## Conclusions

The morphology and particle size of the ceramic, controlled by the preparation method followed in this work, noticeably modifies the behaviour of α-$Al_2O_3$/PLLA/PMMA/IB systems, *i.e.*, ibuprofen release from the composites. Ibuprofen release is facilitated in composites in which the ceramic component has a smaller particle size, with spherical morphology and a homogeneous size distribution.

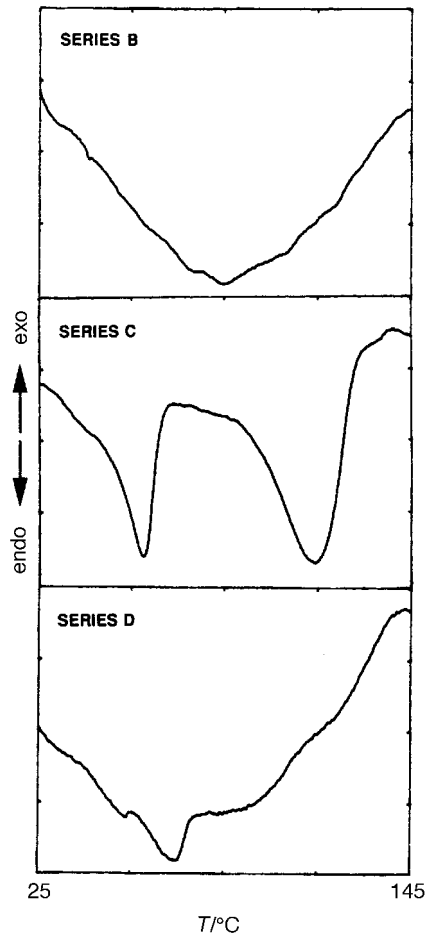


**Fig. 5** DSC curves of composites of series B, C and D with 17 mass% IB (DSC curve of series A is similar to that obtained for series C)

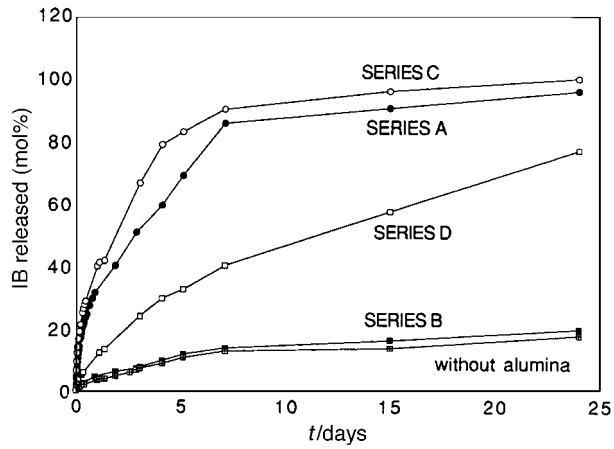


**Fig. 6** Ibuprofen release (mol%) in a buffered solution *vs.* immersion time of composites with 17 mass% IB

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### References

1 L. M. Rodríguez-Lorenzo, A. J. Salinas, M. Vallet-Regí and J. San Roman, *J. Biomed. Mater. Res.*, 1996, **30**, 515.
2 J. B. Park and R. S. Lakes, in *Biomaterials. An Introduction*, Plenum, New York, 2nd edn., 1992.
3 J. B. Park, in *The Biomedical Engineering Handbook*, ed. J. B. Bronzino, CRC Press, Boca Raton, Florida 1995.
4 M. Vallet-Regí, S. Granado, D. Arcos, M. Gordo, V. Ragel, V. Cabanas, A. Salinas, A. L. Doadrio and J. San Roman,

Communication to the *Fifth World Biomaterials Congress*, Toronto, Canada, 1996, II770.
5 R. K. Kulkarni, E. G. Moore, A. F. Hegyeli and F. Leonard, *J. Biomed. Mater. Res.*, 1971, **5**, 169.
6 P. J. Hocking, *Rev. Macromol. Chem. Phys.*, 1992, **C32**, 35.
7 A. J. C. Lee, R. S. M. Ling and J. D. Wrighton, *J. Bone Jt. Surg. A*, 1971, **53**, 759.
8 E. Papirer, J. M. Perrin, G. Nanse and P. Ftoux, *Eur. Polym. J.*, 1994, **30**, 985.
9 Goodman and Gilman's, *The Pharmacological basis of Therapeutics*, Pergamon, New York, 8th edn., 1990, pp. 664–668, 1684.
10 G. Heimke, *Handbook of Biomaterial Evaluation*, ed. A. F. von Recum, McMillan, New York, 1986.
11 A. Pizzoferrato, S. Stea, A. Sudanese, A. Toni, M. Nigrisoli, G. Gualtieri and S. Squarzoni, *Biomaterials*, 1993, **14**, 583.
12 X-Ray Powder Data File, ASTM 43-1484.
13 M. V. Cabanas, M. Vallet-Regı, M. Labeau and J. M. Gonzalez-Calbet, *J. Mater. Res.*, 1993, **8**, 2694.
14 M. Vallet-Regı, L. M. Rodrıguez-Lorenzo, C. V. Ragel, A. J. Salinas and J. M. Gonzalez-Calbet, *Solid State Ionics*, 1997, in press.
15 E. A. Turi, in *Characterization of polymeric materials*, Academic Press, London, 1981.
16 X-Ray Powder Data File, ASTM 13-1723.

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