Preparation, characterization, and *in vitro* release of Ibuprofen from Al_2O_3/PLA/PMMA composites

M. Vallet-Regí,[1] S. Granado,[1] D. Arcos,[1] M. Gordo,[1] M. V. Cabañas,[1] C. V. Ragel,[1] A. J. Salinas,[1] A. L. Doadrio,[1] J. San Román[1,2]

[1]*Departamento de Química Inorgánica y Bioinorgánica, Facultad de Farmacia, UCM, 28040 Madrid, Spain*

[2]*Instituto de Ciencia y Tecnología de Polímeros, CSIC, Juan de la Cierva, 3, 28006 Madrid, Spain*

Received 17 October 1996; accepted 18 March 1997

Abstract: The preparation, characterization, and *in vitro* release of Ibuprofen from Al_2O_3, poly(L-lactic acid) (PLLA), and polymethylmethacrylate (PMMA) composites are described. The release process of the anti-inflammatory drug after the immersion of composites in a buffered solution is analyzed. The rate of Ibuprofen release is related to the crystalline or amorphous form of the drug. The presence of a ceramic component, α-Al_2O_3, and a biodegradable polymer, PLLA, facilitates both Ibuprofen crystallization and drug release. In addition, these composite systems modulate the release of the stereoisomers R(−) and S(+) of the drug. © 1998 John Wiley & Sons, Inc. *J Biomed Mater Res*, **39,** 423–428, 1998.

Key words: composites; ceramic polymer drug; ibuprofen release; alumina; poly(L-lactic acid)

INTRODUCTION

The introduction of active drugs in hard composites used in orthopedic surgery has become one of the most interesting topics in the past few years.[1,2] In particular, the possibility of local delivery of nonsteroidic anti-inflammatory agents such as salicylic acid and several derivatives of phenyl acetic or propionic acids seems to be attractive because they alleviate inflammation when administered orally or by injection. Ibuprofen is perhaps the most representative compound of this series.[3] According to the chemical structure of Ibuprofen, two stereoisomers, S(+) and R(−), are always present in the commercial formulations. However, only S(+) stereoisomer is active. On administration, the R(−) form is inverted to the S(+) form by the organism.[4]

On the other hand, α-Al_2O_3 was the first bioceramic widely used clinically. Its highly bioinert character, excellent corrosion resistance, high wear resistance, and high strength[5] have made it useful as a component in a great number of dental[6,7] and orthopedic applications,[8,9] otorhinolaryngology,[10,11] coatings that provide tissue growth,[12,13] and maxillofacial reconstruction.[14] Polymer–alumina associations have interesting applications owing to their mutual interaction through polar coupling and hydrogen bonding, which provide good adhesion between the ceramic and polymeric components. This is of practical interest in the case of polymeric systems such as poly(L-lactic acid) (PLLA), and poly(methylmethacrylate) (PMMA). These polymers contain carboxylic ester groups in their structures, which could give rise to strong interactions with alumina particles.[15]

In this work, preparation and characterization of composites consisting of a bioinert ceramic, α-alumina, a biodegradable polymer, PLA, a biostable polymer, PMMA, and an anti-inflammatory drug, Ibuprofen, are presented. Controlled release of Ibuprofen stereoisomers from composites was analyzed *in vitro* by means of selective analytic techniques. The idea was the design and preparation of filling biomaterials for orthopedic surgery and dental applications, with inherent anti-inflammatory profiles. Apart from the therapeutic action of the drug, the release of Ibuprofen

Correspondence to: M. Vallet-Regí

Contract grant sponsor: CICYT (Spain); Contract grant number: MAT96-0919

 CCC 0021-9304/98/030423-06

and the resorption of the biodegradable component, PLA, could offer an interesting way for tissular integration of the filling material.

MATERIALS AND METHODS

Reagents and products

Alumina, α-Al_2O_3, was prepared from $Al(NO_3)_3 \cdot 9H_2O$ by thermal treatment, first for 12 h at 400°C, then at 900°C for 24 h, and finally at 1250°C for 33 h. PLLA was prepared by the polycondensation of L-lactic acid in a solution of xylene at 130°C, using *p*-toluenesulphonic and boric acids as catalysts. The average molecular weight was determined by size exclusion chromatography (SEC) giving a value of $\overline{M}_n$ = 3600. MMA was used as received without purification.

Composites of alumina with PLA and PMMA, charged with different amounts of Ibuprofen as the pharmacologically active component, were prepared by the free radical polymerization of a mixture of α-Al_2O_3, PLA, and MMA using a 0.5 wt % of benzoyl peroxide as initiator.[16] Cylindrical specimens (6 mm in diameter and 10 mm in length) were obtained using Teflon molds at a polymerization temperature of 60°C for 24 h.

Characterization

Starting materials and prepared composites were characterized by thermogravimetric and differential thermal analysis (TG-DTA), differential scanning calorimetry (DSC), X-ray diffraction (XRD), and nuclear magnetic resonance spectroscopy (^{1}H-NMR).

The thermal study was carried out in a TG-DTA 320 Seiko thermobalance with a heating rate of 10°C min^{-1} in the range of 25°–500°C. DSC measurements were carried out in a Seiko SSI SSC/5200 at a heating rate of 10°C min^{-1} in the range of 30°–200°C.

^{1}H-NMR spectra were obtained after extraction of the organic components from the composite specimens, using a Varian XL300 spectrometer. The extraction was carried out by the dissolution of PMMA, PLA, and Ibuprofen in hot chloroform for 12 h. The solvent was evaporated at low pressure and the dry residue was analyzed in solution of deuterated chloroform (5 wt/v %) at 40°C, using tetramethylsilane as the internal standard reference.

X-ray data were obtained using CuKα radiation with a Philips X'Pert MPD diffractometer equipped with a multipurpose sample holder for nondestructive analysis of samples which allows the study of crystallinity components distributed randomly in the cylinder.

In vitro release and biodegradation

The release of Ibuprofen after immersion of the cylinders in 20 mL of buffered solution (KH_2PO_4/K_2HPO_4) at pH 7.4 and 37°C, was followed by ultraviolet (UV) spectroscopy, using a Perkin-Elmer 554 spectrophotometer. The analysis was carried out measuring the intensity of the signal at λ_{max} = 264 nm with the time of immersion. For this study, the characteristic maximum of Ibuprofen at 220 nm could not be used because of overlaps with the maxima of other components present in the composite. To minimize experimental errors, the buffered solution was not renovated during the experiment, although this methodology does not simulate conditions in the body.

The release of Ibuprofen was also analyzed by high-performance liquid chromatography (HPLC) with a liquid chromatograph system equipped with a Kontron Station Data (D450 software), two Waters Associated M6000A pumps, a Kontron automatic injector with variable temperature options and a Diode Array Detector LDC SM5000. The release of R(−) and S(+) stereoisomers of Ibuprofen takes place in 2 mL potassium phosphate buffer, pH 7.4, at 37°C. The HPLC conditions were as follows: mobile phase = methanol/Na_2HPO_4 0.01*M* (25%); flow = 1 mL/min; column = spherisorb ODS 5 μm (diameter), 20 cm (length); λ_{max} = 220 nm and oven temperature 50°C. Under these conditions, the retention times of R(−) and S(+) stereoisomers were 2.34 and 2.49 min, respectively.

RESULTS AND DISCUSSION

Reinforced ceramic/polymer composites with specific pharmacologic activity for orthopedic applications were easily prepared by the free radical polymerization of a slurry of Al_2O_3, Ibuprofen, PLA, and PMMA dispersed in monomeric MMA. To study the influence of each component on the delivery process, four series were prepared (Table I). Series A and B were prepared with all four components, i.e., α-Al_2O_3, PLA, PMMA, and Ibuprofen, varying the PLA/PMMA weight ratio (Table I). Series C was prepared without biodegradable PLA, and series D was prepared without ceramic Al_2O_3.

The actual compositions of the prepared systems were determined by two complementary characterization techniques, TGA and ^{1}H-NMR. The content of Al_2O_3 was calculated by TGA, comparing the loss percentage assigned to thermal degradation of organic components, with the weight percentage of the residue at 500°C (identified by XRD as α-Al_2O_3[17]), which gives the actual composition of the ceramic in the specimen analyzed. To check the homogeneous distribution of ceramic components in the composite, thermogravimetric studies were performed on different portions of the cylinders. The differences in composition of these samples were lower than 2 wt %. The average data obtained are shown in the fifth column of Table I.

It is possible to determine the average content of the organic components PLA, PMMA, and Ibuprofen, by means of analysis of the ^{1}H-NMR spectra of the whole

TABLE I
Compositions of Samples Prepared

Series	Wt % PLA Experimental (Theoretical)*	Wt % PMMA Experimental (Theoretical)*	Wt Ibuprofen Experimental (Theoretical)*	Wt % α-Al_2O_3 Experimental (Theoretical)†
A	28 (32)	28 (32)	11 (9)	33 (27)
	24 (29)	24 (29)	25 (17)	27 (25)
B	20 (17)	32 (41)	19 (17)	29 (25)
	38 (41)	19 (17)	16 (17)	27 (25)
C		57 (64)	12 (9)	31 (27)
		51 (58)	23 (17)	26 (25)
D	38 (32)	49 (59)	13 (9)	
	36 (29)	43 (54)	21 (17)	

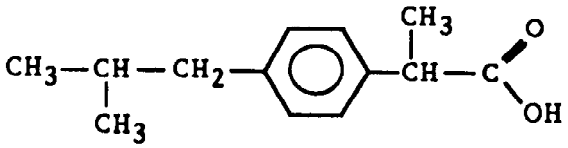
*Determined by ^{1}H-NMR.
†Determined by TGA.

organic fractions isolated as described in the experimental section. Characteristic signals of every component, PLA, PMMA, and Ibuprofen, are assigned in the spectra according to the molecular structure depicted in Figure 1.

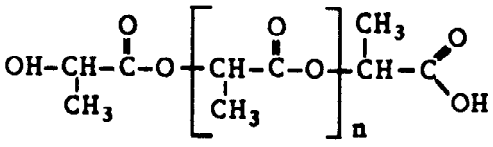
Figure 2 shows the ^{1}H-NMR spectrum of organic fraction of a series A composite prepared with 9 wt % of Ibuprofen. The signal at δ = 7.3–7.1 ppm is assigned to the aromatic protons of Ibuprofen, the signal centered at δ = 5.20 ppm is assigned to the (CH) group of lactic acid units along the polymeric chains, and the small signal at δ = 4.35 ppm is assigned to the (CH) group of lactic acid units at the end of the macromolecular chains. The sharp peak at δ = 3.55 ppm corresponds to the methoxy CH_3O–a group of the MMA units.[18] Comparisons of the integrated intensities of signals provides the average molar composition of the three components with an accuracy of ±2%. The results obtained are shown in Table I.

Figure 3 shows the XRD patterns corresponding to series A, B, C, and D composites with the highest content of Ibuprofen. Series A and B showed maxima diffraction that could be assigned to α-Al_2O_3,[17] Ibuprofen,[19] and PLA (previously characterized by XRD), but in XRD patterns of series C and D, reflections corresponding to Ibuprofen were not observed. This means that Ibuprofen was not able to crystallize under experimental conditions for the preparation of composites C and D, but crystallized easily under conditions of preparation of series A and B. It is necessary to realize that during synthesis of the composites the temperature of the system is higher than the melting point of Ibuprofen and on melting, Ibuprofen no longer retains its crystalline form.

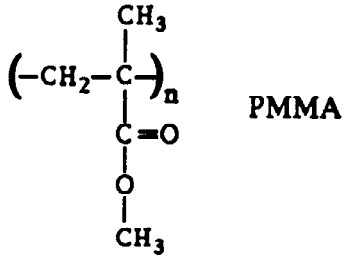
These results are supported by analysis of the samples by DSC. Composition of the samples resulted in different DSC peaks (Fig. 4). The curves of composites of series A and B presented an endothermic peak between 58° and 65°C [Fig. 4(a)], associated with melt-



IBUPROFEN



PLA



PMMA

Figure 1. Molecular structure of organic components of composites.

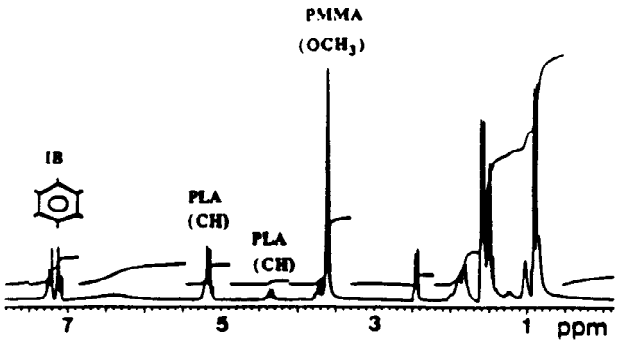


Figure 2. ^{1}H-NMR spectrum of a composite of series A with 9 wt % of Ibuprofen.

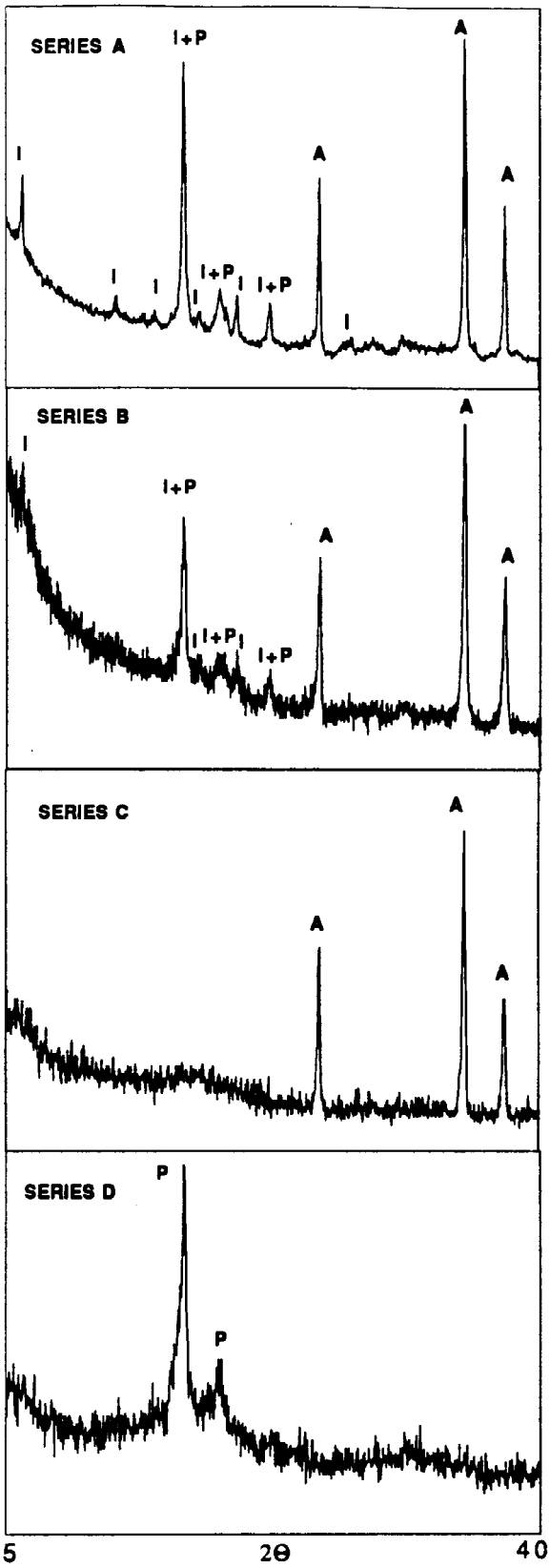


Figure 3. XRD patterns of composites with 17 wt % of Ibuprofen. I = Ibuprofen; P = PLA; A = α-Al_2O_3.

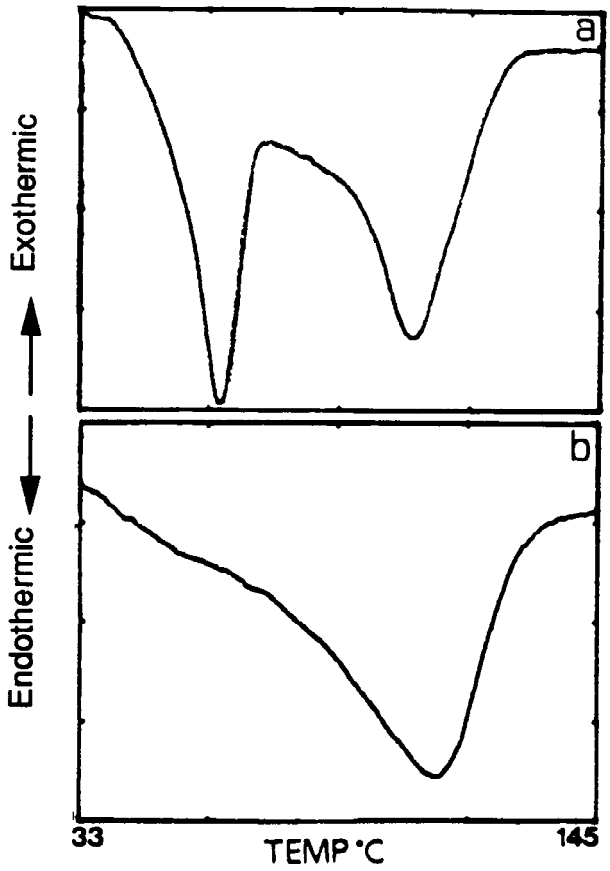


Figure 4. DSC curves of (a) composite of series A with 9 wt % of Ibuprofen and (b) composite of series D with 9 wt % of Ibuprofen.

ing of crystalline Ibuprofen (lower temperature than pure Ibuprofen, 72°C), which was not observed in the DSC curves [Fig. 4(b)] obtained for samples prepared in the absence of PLA or α-Al_2O_3 (series C and D). The second endothermic peak, between 108° and 131°C, observed in all samples, except in series C, corresponded to the melting of PLA (lower temperature than pure PLA, 135°C, previously determined).

In conclusion, during preparation of the composites, the presence of α-Al_2O_3 together with PLA favors the crystallization of Ibuprofen, but if any of these components is absent, the Ibuprofen remains amorphous. The amorphous or crystalline state of the analgesic could noticeably affect the release of Ibuprofen from the corresponding composites. On this basis, the release of Ibuprofen from the composites of different series was analyzed by UV spectroscopy as described in the experimental section.

Figure 5 shows the cumulative release of Ibuprofen for the four series prepared with the highest content of analgesic. It is clear that the release of IB was completely different for composites containing the drug in crystalline or amorphous form. Composites in which Al_2O_3 (series D) or PLA (series C) was absent showed a very slow release and only 18 mol % of drug was

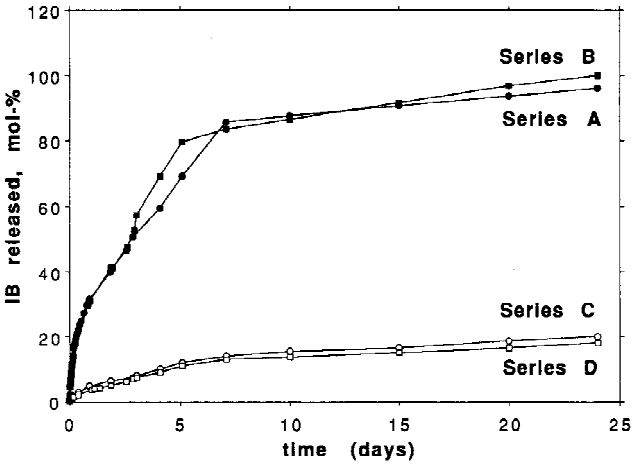


Figure 5. Ibuprofen-released molecular percentage in a buffered solution versus immersion time of composites with 17 wt % of Ibuprofen, measured by UV spectroscopy.

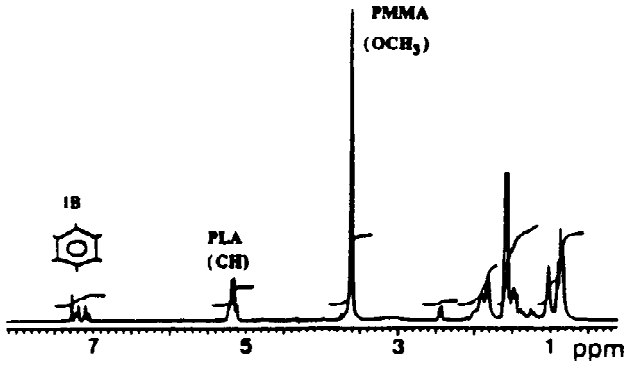


Figure 6. ^{1}H-NMR spectrum of a composite of series A with 9 wt % of Ibuprofen after the immersion of 7 days in buffered solution.

released after 25 days of immersion. However, for the series A and B composites, which contained all the components, a relatively fast initial release was observed. After 6–7 days of dissolution, a constant regime was attained, releasing practically 100 mol % of the charged drug after 25 days.

Results obtained indicate that Ibuprofen was retained in series C and D composites. Ibuprofen present in these composites was in an amorphous state favoring interactions with the carboxylic ester groups of polymeric components PMMA and PLA. These interactions conferred hydrophobicity to the composites. The induced hydrophobicity was probably responsible for the slow release of Ibuprofen from the polymers PLA and PMMA.

After the *in vitro* release of Ibuprofen, composites were characterized by TGA and ^{1}H-NMR spectroscopy obtaining fractions of ceramic and organic components, respectively. The results obtained agree with percentages of Ibuprofen released shown in Figure 5.

Comparisons of ^{1}H-NMR spectra of samples before and after 7 days of immersion in buffered solution (Figs. 2 and 6, respectively) showed a decrease in signals assigned to Ibuprofen (7.0–7.3 ppm) as opposed to the sharp signal of PMMA (3.6 ppm). The signals assigned to end groups of polymeric molecules of PLA (4.45 ppm) weakened considerably owing to the dissolution of macromolecules and low-molecular-weight oligomers in the phosphate buffer.

According to the results obtained by ^{1}H-NMR, it can be confirmed that Ibuprofen release was produced in different percentages depending on the composition of the composites. In addition, it can be observed that in the dissolution test, PLA underwent a fragmentation process.

Estimation of Ibuprofen by HPLC seems to be a better procedure for measuring Ibuprofen, since it also allows measurement of the amounts of stereoisomers of R(−) and S(+) of Ibuprofen released in the potassium phosphate buffer.

The data presented in Figure 7 show that the percentage of Ibuprofen (R + S) estimated by HPLC agree with the data obtained by UV spectroscopy.

Moreover, selective release of both stereoisomers of Ibuprofen was found. As shown in Figure 7, R(−) stereoisomer release was higher than that observed for S(+) stereoisomer. It must be taken into account that only S(+) stereoisomer is the active form. However, within the human body an inversion of the configuration of the R(−) to S(+) takes place.[4]

CONCLUSIONS

Composite systems for surgical applications based on Al_2O_3/PLA/PMMA may be designed as effective devices for the controlled release of anti-inflammatory agents such as Ibuprofen.

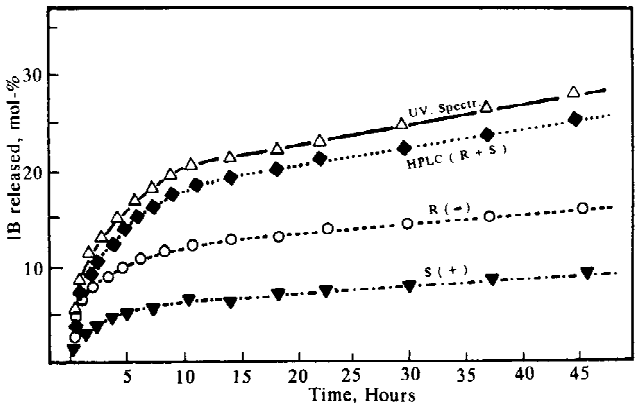


Figure 7. R(−) and S(+) IB stereoisomers released, molecular percentage versus immersion time of a composite of series A with 9 wt % of Ibuprofen, measured by HPLC. A comparison of Ibuprofen released obtained from HPLC and UV spectroscopy is shown.

Ibuprofen release is related to the crystalline or amorphous form of the drug. The presence of a ceramic component, Al_2O_3, and a biodegradable polymer, PLA, facilitates both Ibuprofen crystallization and drug release.

The composite systems modulate release of the stereoisomers R(−) and S(+) of the drug.

References

1. P. K. Bajpai and W. Billotte, ''Ceramic biomaterials,'' in *Biomedical Engineering Handbook,* J. D. Bronzino (ed.), CRC Press, Boca Raton, FL, 1995, pp. 552–580.
2. J. Kost, ''Biomaterials in drug delivery,'' in *Encyclopedic Handbook of Biomaterials and Bioengineering,* D. L. Wise, D. J. Trantolo, D. E. Altobelli, M. J. Yaszemski, J. D. Gresser, and E. R. Schwartz (eds.), Marcel Dekker, New York, 1995, p. 1201.
3. L. S. Goodman and A. Gilman, *The Pharmacological Bases of Therapeutics,* 8th ed., Pergamon Press, New York, 1990, pp. 664–668, 1684.
4. H. Cheng, J. D. Rogers, J. L. Demetriades, S. D. Holland, J. R. Seibold, and E. Depuy, ''Pharmacokinetics and bioinversion of ibuprofen enantiomers in humans,'' *Pharm. Res.,* **11,** 824–830 (1994).
5. L. L. Hench, ''Bioceramics: From concept to clinic,'' *J. Am. Ceram. Soc.,* **74,** 1487–1491 (1991).
6. R. R. Seghi, T. Daher, and A. Caputo, ''Relative flexural strength of dental restorative ceramics,'' *Dent. Mater.,* **6,** 181–184 (1990).
7. K. Arvidson, B. Fartash, L. E. Moberg, R. Grafstrom, and I. Ericsson, ''In vitro and in vivo experimental studies on single crystal sapphire dental implants,'' *Clin. Oral Implants Res.,* **2,** 47–55 (1991).
8. A. Pizzoferrato, S. Stea, A. Sudanese, A. Toni, M. Nigrisoli, G. Gualtieri, and S. Squarzoni, ''Morphometric and microanalytical analyses of alumina wear particles in hip prostheses,'' *Biomaterials,* **14,** 583–587 (1993).
9. L. Sedel, ''Total hip prosthesis in young patients,'' *Rev. Prat.,* **44,** 1580–1586 (1994).
10. K. H. Chan, J. S. Reilly, and Y. Hashida, ''A staged laryngotracheal reconstruction using alloplast (Proplast) in the canine model,'' *Int. J. Pediatr. Otorhinolaryngol.,* **18,** 227–239 (1990).
11. K. Jahnke, ''New ceramic implants for reconstruction of the ear ossicle chain,'' *Laryngorhinootologie,* **71,** 1–4 (1992).
12. Y. Kakutani, T. Yamamuro, T. Nakamura, and Y. Ktoura, ''Strengthening of bone–implant interface by the use of granule coatings on alumina ceramics,'' *J. Biomed. Mater. Res.,* **23,** 781–808 (1989).
13. T. Inadome, K. Hayashi, Y. Nakashima, H. Tsumura, and Y. Sugioka, ''Comparison of bone–implant interface shear strength of hydroxyapatite-coated and alumina-coated metal implants,'' *J. Biomed. Mater. Res.,* **29,** 19–24 (1995).
14. J. H. Dubruille, G. Chomette, S. Vanhakendover, M. Vanhakendover, and E. Viguier, ''Contribution to the experimental study of endosseous sintered ceramic implant,'' *Rev. Stomatol. Chir. Maxillofac.,* **91,** 70–72 (1990).
15. E. Papirer, J. M. Perrin, G. Nanse, and P. Ftoux, ''Adsorption of poly(methylmethacrylate) on an α-alumina: Evidence of formation of surface carboxylate bonds,'' *Eur. Polym. J.,* **30,** 985–991 (1994).
16. L. M. Rodríguez-Lorenzo, A. J. Salinas, M. Vallet-Regí, and J. San Román, ''Composite biomaterials based on ceramic-polymers. I. reinforced system based on Al_2O_3/PMMA/PLLA,'' *J. Biomed. Mater. Res.,* **30,** 515–522 (1996).
17. X-ray powder data file, ASTM 43-1484.
18. Q. T. Pham, R. Petiaud, H. Waton, and M. F. Llamo, *Proton and Carbon Spectra of Polymers,* Vol. 3, Wiley, New York, 1984, p. 52.
19. X-ray powder data file, ASTM 13-1723.