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CERAMIC BIOMATERIALS: AN INTRODUCTORY OVERVIEW

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ABSTRACT

A review of classes of biomaterials and their applications is presented. Particular interest is paid to bioceramics, calcium phosphates and hydroxyapatite which are the leading biomaterials employed today. Several methods for producing hydroxyapatite are presented, including the characteristics and disadvantages of each methodology reported in specialized literature. The main trends of the modern biomaterial science and technology, as well as the fundamental scientific problems involved, are discussed.

Keywords: *ceramic; biomaterials*

INTRODUCTION

Biomaterials have become a 'fashionable' and very active area of research and development in Materials Science and Engineering (MSE) worldwide. Each year witnesses the creation of new journals specialized in this or in related subjects. The reasons for this fascinating area to grow so fast are complex. However one can name some of the most relevant aspects of Biomaterials Science and Technology that make the field so attractive. First of all, the need to do interdisciplinary work when addressing a specific problem in this area has led many researchers, spanning from public health specialists to the so-called hard sciences investigators, to have fruitful exchanges from areas others than their original field. Second, because biomaterials oblige to study in detail some fundamental problems that are common to many sciences. Many difficulties when preparing or characterizing biomaterials lie in the basic physical-chemical or even mathematical phenomena. Third, and perhaps the main motivation for many private corporations, because biomaterials represent a potential market of several million dollars a year, and any innovation proven to be adequate for a particular problem constitutes a very attractive profit. This situation is far from

being reflected in current instruction in MSE - the fact which behooved us to write the present article.

The word 'biomaterial' itself is loosely employed for describing a wide variety of materials used for biomedical applications. Arguments still arise on where exactly the boundary lies between an authentic biomaterial and a biomedical device. In fact, many polymeric materials that are utilized as parts of a complicated kidney replacement, for instance, could or could not be regarded as a biomaterial, depending on the working definition of the term. Nevertheless, calcium-based compoundsincluding carbonates and phosphates are the rising stars of biomaterials, at least in terms of the growing number of articles, patents and designs that are issued annually. The attraction to these particular materials has several aspects of its own, including without a doubt, commercial interests of certain powerful companies. As we shall see in what follows, however, the basic technical reason for the preference for calcium-based compounds lies in the fact that a bone is formed largely by calcium phosphates, among which hydroxyapatite (HAp) has received special attention.

The currently used definition, formulated by the 6th Annual International Biomaterials Symposium is: " a biomaterial is a systemically, pharmacologically inert substance designed for implantation within or incorporation with a living system"[1]. In 1986 The European Society for Biomaterials Consensus Conference provided a somewhat similar definition: "a biomaterial is a substance or material used alone or in the fabrication of a medical device designed to interact with human tissues to monitor body functions or to deal with pathological conditions of the body" [2,3]. Biocompatibility means not only that the material causes no harm to the body but also that the surrounding tissues do not alter the material. A material is "*not biocompatible"* if it is toxic or causes death of the surrounding tissues [4].

The development of new technologies has provided ceramic materials with physical, mechanical and chemical properties that make them very suitable for orthopedic and dental implants. In modern medicine, biomaterials are mainly used in orthopedic surgery, maxillo-facial surgery, cardiovascular surgery and ophthalmology. Accordingly, we provide bellow a review of the main technologies available for synthesizing or preparing HAp from various sources, we emphasize the advantages and disadvantages of each methodology, in terms of the present and future trends in the biomaterial science and technology.

TYPES OF BIOMATERIALS

According to the surgical uses, biomaterials with a variety of properties are needed. Table I contains a broad list of biomaterials, their advantages and disadvantages, and examples of their applications.

Thus, polymers are used when complex forms or high flexibility are needed, metals when the implant will suffer high mechanical loads, while composites are used to improve the interaction with the tissues.

The importance of ceramics is growing due to their biocompatibility, resistance to corrosion and mainly because an important part of bones themselves are mineral phases. Therefore, ceramics are used as bone substitute or to promote bone regeneration.

Natural materials are preferred due to their availability and because the problem of rejection is eliminated, particularly when they come from the same patient.

Table I. Types of Biomaterials, characteristics and applications [1,3,5]

Material	Advantages	Disadvantages	Main Applications
Polymers: Silastic®, Teflon®, Dacron®, Nylon, PMMA, Polyethylene, Polypropylene, Polytetrefluorethylene	Easy to produce, low density	Low mechanical resistance, easily degradable	Sutures, arteries, veins, cements, artificial tendons, teeth, ears, nose, heart valves, lenses, testicles and breasts. implants
Metals: Steels 316, 316L, Vitallium®, Silver, Tantalum Cobalt F-75 and alloys of: Ti, Cr+CO, Cr+Co+Mo	Ductility, high mechanical resistance to wear and shock	Low biocompatibility, corrosion in a physiological environment, mechanical properties very different from those of biological tissues	Staples, plaques and wires, articulation prosthesis, tooth implants, penis implants, skull plaques and mesh for face reconstruction
Ceramics: Aluminum oxides, calcium aluminates, titanium oxides, calcium phosphates, carbon, Bioglass®	High biocompatibility, corrosion resistance, high resistance to compression, inert, low thermal and electrical conductivity	Low impact resistance, properties difficult to reproduce, difficulties in processing and fabrication	Dental parts, coatings, bone fillings, endoscopy, otologic implants, medical tools and equipment
Composites: Metals with ceramic coatings, materials coated with carbon	High biocompatibility, corrosion resistant, inert	Lack of consistency and difficult to reproduce during fabrication	Heart valves, knee implants, artificial articulations, hip implants
Natural Materials: Colagen, human tissues, hialuronic acid, grafts	Availability in the human body, biocompatibility	Possible rejection by host	Increase or substitution of hard and soft tissues, cornea protectors, vascular grafts, tendons and ligaments, heart valves, ophthalmologic lubricants, substitution of synovial fluid

Table II. Unit prices for several biomaterials and implants [8]

Biomaterial / implant	Company	Price (in US$)
HAp spheres	Integral Orbital Implants	800
Titanium foil for implants	STERI-OSS®	180
HAp coated Titanium foil	STERI-OSS®	180
HAp bone filling OsteoGraf®	STERI-OSS®	200-720
Bone filling (HAp w/ PGA)	STERI-OSS®	125-235
Porous bone graft (from cattle, 5 gr)	BIO-OSS®	375
Cortical bone graft (from cattle, 5 gr)	BIO-OSS®	317
Synthetic HAp particles (4 and 12 gr)	OsteoGraf®	120-420
HAp flexible segments (6x38 mm)	PermaRidge®	245

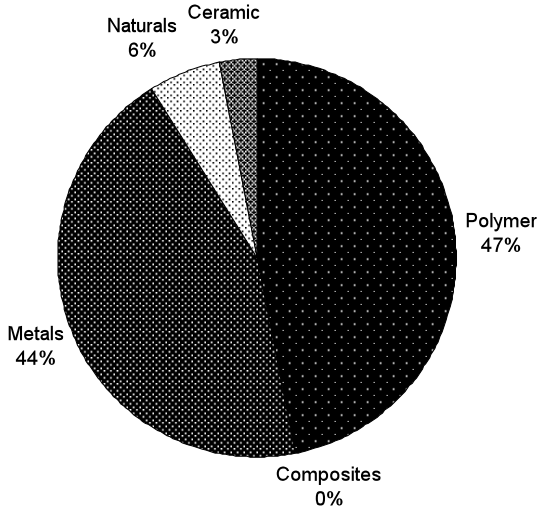

Figure 1. Total sales 1987 (M$4,700)

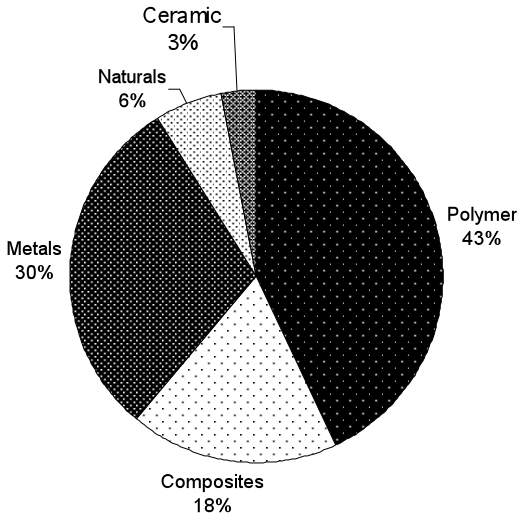

Figure 2. Total sales estimated for 2002 (M$ 11,700)

GLOBAL BIOMATERIALS MARKET [3,6,7]

Biomaterials sales at world level in 1987 were M$ 4,700. The estimates for year 2002 are M$ 11,700, almost triple than in 1987 (see Fig.1 and 2). The largest share corresponds to polymers, mainly because polymers are displacing metals due to production methods, characteristics and low cost; polymer demand is growing faster than production. As for metals, sales have increase because surgeons prefer long lasting materials, but their percentage of total sales decreases. Composites are still under clinical evaluation with encouraging results; if sales increase in the near future as estimated they might also further diminish the share currently taken by metals. The use of natural materials shows a constant percentage.

Ceramics include a variety of biomaterials, such as calcium and carbon phosphates and alumina. Both surgeons and researchers have shown great interest in them, but market applications are still under search. In this group hydroxyapatite (HAp) has a dominant place, being used for oral and maxillo-facial surgery as bone substitute and as coating for metal and carbon implants. Sales are expected to jump from M$128 in 1987 to M$344 in 2002.

Table II shows the 2000 price for several commercial ceramic biomaterials.

BONE TISSUE

Although the amount of elements varies for different parts of the skeleton, bones contain about 2/3 of inorganic and 1/3 of organic materials. The mineral phase constitutes 69 % of the total weight, with 9 % water and 22 % corresponding to the organic matrix.

Table III lists several calcium phosphates. HAp is found in different parts of the body as a constituent of various types of calcified tissues. Calcified tissue include tooth enamel (95 % HAp), dentin (75 % HAp) and cement (35 % Hap); the bone contains an organic part and an inorganic part (70 %) which includes HAp and tri calcium phosphate.

The mineral phase of the bone is mainly made up of calcium phosphate micro-crystals, among them hydroxyapatite is the most important, its chemical formula reads $Ca_{10}(PO_4)_6(OH)_2$.

Table III. Calcium Phosphates

Amorphous calcium phosphate (ACP)	$Ca_3(PO_4)_{2n}H_2O$
Brushite	$CaHPO_4H_2O$
Octacalcium phosphate (OCP)	$Ca_8H_2(PO_4)_65H_2O$
Whitlockite	$Ca_3(PO_4)_2$
Hydroxyapatite	$Ca_{10}(PO_4)_6(OH)_2$.

Other mineral phases include di-calcium phosphate $Ca_2P_2O_7$, di-basic calcium phosphate $CaHPO_4$, tri-calcium phosphate $Ca_3(PO_4)_2$ and several amorphous phases of calcium phosphates. There are also ions present such as citrate, carbonate, fluoride and hydroxyl, which produce small microstructural differences in bone tissue. Some impurities might be found, including magnesium, sodium, and traces of chlorine and iron [1]. It is worth mentioning that at the human body temperature and pH only HAp and di-calcium phosphate $Ca_2P_2O_7$ are chemically stable [9].

Table IV shows a comparison between natural and synthetic HAps, including differences in crystallinity.

From the standpoint of biology, bone's connective and structural functions are well known[1,12]. From the Materials Science viewpoint, they are composites that show flexibility and a great capacity to absorb impacts [13,14].

BIOCERAMICS

In general, ceramics show high biocompatibility, high resistance to corrosion, high resistance to compression and low electrical and thermal conductivities. These characteristics make them very suitable for implants. The first reported implant dates from the end of the XIX century[15].

As mentioned earlier, a characteristic of prime interest is low toxicity and the fact that HAp promotes the formation of new bone tissue [1,2,16].

While different processes for obtaining HAp will be discussed below, some general properties of ceramics due to their covalent or ionic bonds[17] are worth to mention. Among them: high fusion temperature, hardness, brittleness, low thermal and electrical conductivities and low chemical reactivity.

Table IV : Weight % for enamel, dentine, bone and synthetic HAp[10,11]

	Tooth enamel	Dentine	Bone	Synthetic HAp
Calcium	36.1	35.0	35.5	39.0
Phosphorus	17.3	17.1	17.1	18.5
Carbon dioxide	3.0	4.0	4.4	-
Magnesium	0.5	1.2	0.9	-
Sodium	0.2	0.2	1.1	-
Potassium	0.1	0.07	0.1	-
Chlorine	0.3	0.03	0.1	-
Fluorine	0.016	0.017	0.02	-
Sulfur	.01	0.2	0.6	-
Zinc	0.016	0.018	-	-
Silicon	0.003	-	0.04	-
atomic ratio Ca/P	1.62	1.59	1.71	1.667
Crystallinity	70-75	33-37	33-37	80-100

Important also is the observation that implants from porous ceramics of HAp very rapidly show invasion of connective tissue [2,18,19].

Calcium phosphates

As mentioned earlier, the inorganic phase of the bone tissue is primarily composed of calcium

phosphates [1,2,10,20,21]. A significant influence in bone tissue regeneration is given to phosphate salts [22] because their physical, chemical and structural properties are very similar to those of bone tissue.

During the 1920's these materials were available only as powders and they were used purely as filling materials. It was soon found, however, that they promote the formation of new bone tissue, particularly when the atomic ratio for these salts is between 1.5 and 1.7 [2,10,21].

Success of calcium phosphates *in vivo* implants depends on several factors, but very important ones are the Ca/P atomic ratio, the porosity and the crystalline structure.

Hydroxyapatite

In general, chemical compounds with the formula $M_{10}(XO_4)_6Z_2$, where M^{2+} is a metal, with the anions XO_4^{3-} and Z^- are known as 'apatites'. The particular name for each apatite depends on the elements or radicals M, X and Z. Consequently, hydroxyapatite (HAp) has the molecular structure in which M is calcium (Ca^{2+}), X is phosphoros (P^{5+}) and Z represents the hydroxyl radical (OH^-). Stoichiometric HAp shows an atomic ratio Ca/P= 1.67 [20]. It crystallizes largely in the hexagonal system, but exceptionally in the monoclinic system [22,23]. The hexagonal system belongs to the space group $P6_3/m$, showing an hexagonal rotational symmetry and a reflection plane with lattice parameter a = b = 0.9418 nm, and c = 0.6884 nm. The monoclinic structure shows a P_2l/b with lattice parameters a = 0.941 nm, b = 0.2nm and c = 0.688 nm, and angles $\alpha=\beta=90°$, $\gamma=120°$. It comprises two HAp molecules: ($Ca_{10}(PO_4)_6(OH)_2$). This structure has not been observed in tissues of living creatures.

Structural substitutions are possible, creating different kinds of hydroxyapatites, including the following ones:

- *Fluoroapatites:*

$Ca_{10}(PO_4)_6(OH)_{2-x}F_x$ $0<x<2$

- *Carbonated hydroxyapatite:*

$Ca_{10}(PO_4)_6(OH)_{2-2x}(CO_3)_x$ $0<x<2$

$Ca_{10-x+y}(PO_4)_{6-x}(CO_3)_x(OH)_{2-x+2y}$ $0<x<2$, $0<y<x/2$

- *Hydroxyapatite with sodium:*

$Ca_{10}Na_{2x/3}(PO_4)_{6-x}(CO_3)_x(H_2O)_y(OH)_{2-x/3}$ $0<x<3$, $0<y<x$

In the first case, F atom substitutions improve the chemical stability, this is the reason for F apatite applications in dental treatments.

It is worth mentioning that in living organisms HAp is not stoichiometric, it does not have a ratio Ca/P <1.67. While HAp is more stable the closer this ratio is to 1.67, the lower this ratio the larger is the bioactivity. Reactivity depends also on the degree of crystallinity.

Apart from the HAp ions and radicals, natural bones show traces of CO_3, Mg, Na, F and Cl; (see Table IV).

METHODS TO OBTAIN HAp

The first report of a method to obtain Hap goes back to 1851[24]. Generally speaking, the traditional methods for producing HAp [1,2,20,24] can be classified as:

Solution procedures [25,26]

In this case solutions with various sources of phosphate and calcium chemical groups are employed. Typically the HAp crystallites are produced by precipitation. The basic method is extremely simple and involves inexpensive equipment, to the extent that precipitating HAp can be a laboratory experiment for students. However, the control of the crystal size represents a difficulty, in spite of some recent developments in which microwaves have been successfully employed. The main disadvantage of all the solution methods proposed so far is the presence of metastable phases in the final product of the reaction. In fact, even some commercial HAp synthesized via solution have appreciable amount of other phosphates and compounds, detrimental to the performance of

the substance as a biomaterial. Also, it is very difficult by these methods to account for the amount of amorphous phases present; the long term chemical stability of the product is also a limiting factor. In general, the solution methods are among the main methods for producing HAp as biomaterial at an industrial or semi-industrial scale, and this situation is expected to remain until a process competitive from the economic standpoint arises as a serious and reliable source for HAp.

Solid State Methods[27-32]

These methods have been explored for their convenience in avoiding some undesirable phases in preparing calcium phosphates. Some recent experiments also show the feasibility of producing good quality HAp from very cheap raw materials (gypsum, for example) which could make the solid state route a serious challenger for the solution industrial synthesis. The main disadvantage in this case is the energy consumption of the procedure and the fact that they can provide easily only relatively large crystallites, due to the crystal growth involved during the reactions. One important issue in this approach, however, is the recent discovery that many of the reactions in solid state which produce HAp include the production of CO_2 as a by-product. This gas can be conveniently exploited as a way for producing controlled porosity in the final product. The possibility of producing composites by in-situ reactions also seems to have interesting potential in the area of biomaterials.

Hydrothermal systems [24, 33, 34]

These procedures have been successfully employed in the past for producing large amounts of industrial ceramics and materials, others than phosphate-based biocompatible compounds. The traditional disadvantage of standard hydro-thermal methods is the poor control of all the variables and, above all, the limitation of creating only relatively large particles (of the order of several microns). The current technology allows the precise control of the corresponding thermodynamical parameters involved, and recent reports show the possibility of producing nanometer-sized calcium phosphates, through the use of microwaves for aiding the process and also via, the synthesis route, producing at will stoichiometric or calcium-deficient HAp. This opens interesting possibilities for scaling the process. In any case, this field is expected to attract more attention of the specialists and more activity will probably be witnessed in the near future.

Novel Developments

We shall now discuss novel developments in the synthesis and processing of HAp [35-43]. Up to quite recently, the main focus of the efforts in biomaterials was the inexpensive synthesis of HAp, which was thought to be nearly the only biomaterial acceptable for bone implants or augmentation. Accordingly, the pioneering works in modern biomaterial science and technology were originated in the USA and England, where the classical studies of calcified tissue motivated the interest of scientists worldwide. Slowly, people have realized that the *spatial structure* plays a key role, perhaps even more than the detailed chemical structure of the biomaterial, especially in the case of bone. This remains to be completely understood.

The first attempts to obtain the right structure involved using a pre-existing framework, which is found in some marine invertebrates such as coral or the so-called sand dollar. The fact that those skeletons are mainly composed from calcium carbonate led some groups to devise hydrothermal methods for converting calcium carbonate into calcium phosphate, while preserving the spatial (i.e. porous) structure, which constitutes itself an interesting scientific problem. Other investigations, however, demonstrated that even carbonates were potentially useful by themselves, provided the correct 3-D structure was present. The success of those technologies is reflected in the commercial coral HAp, offered by American, French, Japanese and Cuban corporations. The potential environmental hazard of destroying

coral reefs, a matter of bitter discussion, has led a Mexican-Spanish group to develop alternative techniques for employing calcium carbonates and phosphates from sea stars, an enormous source for raw materials for the synthesis.

A different possible approach to produce adequate materials involves a convenient use of the escaping CO_2 gas in some solid state reactions, as mentioned above, for producing a bread-like porous structure. Also, some reports on the use of polyelectrolyte cements, modified with alumina and HAp, have been quite successful in producing artificial eye balls.

The complexity of the hierarchical porosity of a real bone has not been taken into account yet in a satisfactory way. A Mexican-Canadian invention for producing HAp tapes and multilayer systems, with controlled porosity and stoichiometry, is basically the only report that could help in reproducing complicated calcified shapes such as the ear bones or the orbit carcass. These represent urgent reconstruction surgery needs.

On the other hand, the low temperature production of HAp and carbonates in a simulated body fluid within an inorganic gel, work pioneered by the Japanese and pursued further in Mexico[44-47], opens exciting possibilities not only for producing in-situ implants, but also for discovering how to produce ceramic materials at nearly room temperature, an area of MSE which seems to have a promising future.

CONCLUDING REMARKS

Biomaterials constitute a lively area of research and development and continue to offer many possibilities. In fact, beyond the technical details of producing materials with tailored characteristics, the field poses some of the very basic questions that are left to answer to the turn-of-the-century Science. Questions such as: how an organically-organized body is able to produce inorganic phases? how a ceramic is produced at body temperature? what are the fundamentals reasons for the complex spatial and physical-chemical organization of biomaterials? etc., still remain to be properly addressed and open virtually endless possibilities for scientists and engineers. To give just one example, the human or animal body produces Hap at 37º C while most man-developed processes require high temperature-with corresponding energy costs.

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REFERENCES

1. J. B. Park, *Biomaterials Science and Engineering*, Plenum Press, New York, 1984.
2. Ravaglioli and A. Krajewski, *Bioceramics; Materials Properties and Applications*, Chapman and Hall, London, 1992.
3. K. Mattox, *Biomaterials- Hard Tissue Repair and Replacement*, vol. **3** (D. Muster, Editor), Elsevier, Amsterdam, 1992.
4. L. L. Hench, *J. Am. Ceram. Soc*. **74**, 1487 (1991).
5. J. E. Lemons, *Perspectives on Biomaterials, Materials Science Monographs*. No 33 (O. C. Lin and E. Y. S. Cho, Editors) Elsevier, Amsterdam, 1986.
6. D. F. Williams, *Adv. Mater. Tech. Monitor* **1**, No 2 (1994).
7. PolySort News Service, Norwalk, Conn., February 1996.
8. E. Rivera, Ph.D. Thesis, Universidad Nacional Autónoma de México, Mexico City, 1997.
9. W. F. Newman and M. W. Newman, *The Chemical Dynamics of Bone Mineral*, The University of Chicago Press, Chicago, 1958.
10. L. Lacout, in *Biomaterials- Hard Tissue Repair and Replacement*, vol. **3** (D. Muster, Editor), Elsevier, Amsterdam, 1992.

11. R. Z. LeGeros, *Hydroxyapatite and Related Materials*, (P. W. Brown and B. Constantz, Editors), CRC Press, Boca Raton, FL, 1994.
12. G. Lewis, *J. Mater. Ed*. **12,** 197 (1990).
13. Miller and J. S. Wray, *Nature* **230**, 437 (1971).
14. N. Natali and E. A. Meroi, *Biomaterials* **11,** 266 (1989).
15. K. de Groot, *Biocompatibility of Clinical Implant Materials*, vol. 1, (D. F. Williams, editor), CRC Press, Boca Raton, FL, 1981.
16. D. F. Williams, *Materials Science and Technology*: *A Comprehensive Treatment*, *Medical and Dental Materials*, vol. 14 (R. W. Cahn, P. Haasen, E. J. Kramer, editors, D. F. Williams, vol. editor), VCH, New York, 1991.
17. D. Bernache-Assolant, *Biomaterials- Hard Tissue Repair and Replacement*, vol. 3 (D. Muster, Editor), Elsevier, Amsterdam 1992.
18. L. Shields, J. A. Shields, R. C. Eagle and P. De Potter, *Am. J. Ophtalm*. **111**, 363 (1991).
19. P. J. Ferrone and J. J. Dutton, *Ophtalmology* **99,** 376 (1992).
20. D. H. Khon and P. Ducheyne, *Materials Science and Technology: A Comprehensive Treatment*: *Medical and Dental Materials*, vol. **14** (R. W. Cahn, P. Haasen, E. J. Kramer, editors, D. F. Williams, vol. editor), VCH, New York, 1991.
21. K. deGroot, C. P. A. T. Klein, J. G. C. Wloke and J. M. A. Blieck-Hogervorst, *Handbook of Bioactive Ceramics,* vol **II** (T. Yamamuro, L. L. Hench and J. Wilson, editors), CRC Press, Boca Raton, FL, 1990.
22. M. I. Kay, R.A. Young and A. S. Posner, *Nature* **204**, 1050 (1964).
23. J. C. Elliot, P. E. Mackie and R. A. Young, *Science* **180**,: 1055 (1973).
24. M. Yoshimura and H. Suda, *Hydroxyapatite and Related Materials,* (P. W. Brown and B. Constantz, Editors), CRC Press, Boca Raton, FL, 1994.
25. H. Monma and Y. Kamiya, *J. Mater. Sci.* **22**, 4247 (1987).
26. Y. Fang and D. M. Agrawal, *J. Mater. Res.* **7**, 8 (1992).
27. J. Black, in Biological Performance of Materials, Fundamentals of Biocompatibility, 2nd. ed, Marcel Dekker Inc. New York, 1992. p.3.
28. S. Hubert, J. Klawiter, R. Leonard, Medical Enginnering Textbook, edited by C. Ray, Year Book Med. Pub. Chicago, 1971.
29. R.Z. LeGeros, *Adv. Dent. Res*. **2**, 164 (1988).
30. R.Z. LeGeros, *Calcium Phosfates in Oral Biology and Medicine,* ed. H. M. Meyrs, Karger, New York, 1991.
31. Arita, D. Wilkinson, M. Mondragon and V. M. Castaño, Biomaterials **16**, 403 (1995).
32. Arita, D. Wilkinson and V. M. Castaño, *J. Mater. Sci.* Med. **6**, 19 (1994).
33. C. Lavenia, *Amer. Ceram. Soc. Bull.* **70**, 95 (1991).
34. M. N. Helmus, *Mater. Res. Soc. Bull*. **16**, 33 (1991).
35. D.M.Roy, S.K. Linnehan, *Nature* **274**, 220 (1974).
36. C. Kasprek, R. Ewers: *Z. Zahnaertl Implantol* **2,** 242 (1986).
37. G. Guillemin, J. L. Patat, J. Fournie, M. Chetail, *J. Biomed. Mater. Res.* **21**, 557 (1987).
38. C. Kasperk, R. Ewers and B. Simons, *Int. J. Oral Masillofac. Surg.* **17**, 319 (1988).
39. E. M. Pinholt, I. E. Ruyter, H. R. Haanaes and G. Band, *J. Oral Maxillofac. Surg.* **50**, 859 (1992).
40. Arita, Ph. D. Thesis , CICESE, Universidad Nacional Autónoma de México, Ensenada, Baja California, 1995
41. R. Rodriguez, J. Coreno, J. Arenas and V. M. Castaño, *Adv. Composites Lett.* **5**, 25 (1996).
42. M. Araiza, J. Portilla, J. C. Hernandez, I. Arita and V. M. Castaño, *Ceram. Trans.* **63**, 27 (1996).

43. V. M. Castaño, D. Suarez, E. Rivera, M. Estevez and J. C. Hernandez, *Ceram. Trans*. **63**, 49 (1996).
44. P. Li, C. Ohtsuki, T. Kokubo, K. Nakanishi and N. Soga, *J. Am. Ceram. Soc.*, **75**{8}, 2094 (1992).
45. P. Li, C. Ohtsuki, T. Kokubo, K. Nakanishi, N. Soga,T. Nakamura and T. Yamamuro, *J. Mater. Sci. Med.*, **4**, 127 (1993).
46. V. M. Castaño, D. Suarez, E. Rivera, M. Estévez and J. C. Hernández, *Ceram. Trans.* **53**, 49 (1996).
47. E. Rivera, M. Bonilla, R. Hernández, R. Rodríguez and V. M. Castaño, *J. Mater. Synth. and Processing* **5**, 153 (1997).