物材料与组织工程

Biomaterials and Tissue Engineering

主编　时东陆

清华大学出版社

北　京

内 容 简 介

本书是“生物材料和生物技术”丛书中的第 1 本。本套书提供了在生物材料和生物技术领域至今最新的信息。它的重点是阐述在这些领域的基本原理和最近的发展。本书共有 5 章,分别是:生物活性材料、材料的生物适应性、无机玻璃的生物学应用、对于生物工艺学的生物合成材料以及细胞组织工艺学。该书可作为材料、生物等相关专业大学高年级学生及研究生的教材,也可供科研人员阅读。

图书在版编目**(CIP)**数据

生物材料与组织工程/ 时东陆主编 . —北京:清华大学出版社,2004
ISBN 7-302-05881-4

Ⅰ.生… Ⅱ.时… Ⅲ.生物材料 Ⅳ.Q81

中国版本图书馆 CIP 数据核字(2002)第 071715 号

出 版 者: 清华大学出版社　　地　　址: 北京清华大学学研大厦
http:// www .tup .com .cn　　邮　　编: 100084
社 总 机: 010-62770175　　客户服务: 010-62776969
责任编辑: 张兆琪
印 装 者: 三河市印务有限公司
发 行 者: 新华书店总店北京发行所
开　　本: 153×235　印张: 16 .25　插页: 2　字数: 374 千字
版　　次: 2004 年 3 月第 1 版　2004 年 3 月第 1 次印刷
书　　号: ISBN 7-302-05881-4/ Q · 26
印　　数: 1～2000
定　　价: 58 .00 元

本书如存在文字不清、漏印以及缺页、倒页、脱页等印装质量问题,请与清华大学出版社出版部联系调换。联系电话: (010)62770175-3103 或(010)62795704

Contents

此为试读,需要完整PDF请访问: www.ertongbook.com

List of Contributors

Donglu Shi

Department of Materials Science and Engineering, University of Cincinnati
Cincinnati, OH 45221-0012, USA
Email: Dshi@uceng.uc.edu

Alexis Clare

Director, Industry-University Center
for Bioceramics
Alfred University, USA
Email: clare@alfred.edu

Min Wang

Medical Engineering and
Mechanical Engineering
Faculty of Engineering
University of Hong Kong
Pokfulam Road, Hong Kong
Email: minwangbiomats@yahoo.co.uk

Toshihiro Kasuga

Graduate School of Materials
Science and Engineering
Nagoya Institute of Technology
GoKiso-Cho, Showa-Ku
Nagoya 466-8555, Japan
Email: kasugato@mse.nitech.ac.jp

Miqin Zhang

302L Roberts Hall
Department of Materials Science and Engineering University of Washington
Seattle, WA 98195-2120, USA
Email: mzhang@u.washington.edu

Qing Liu

Celgene Cellular Therapeutics
Division 45 Horse Hill Road,
Suit 110 Cedar Knolls,
NJ 07927 USA
Email: qingliu@yahoo.com

Bioactive Materials and Processing

Min Wang

1.1 Introduction

It is widely recognized that the rapid and continuing change in emphasis in materials science away from traditional engineering materials has been largely instituted by the requirements of emerging technologies for advanced and structurally sophisticated new materials. Medical engineering, often included in the list of advanced technologies, requires the underpinning of high-tech materials. The word which is used to categorize materials for biomedical applications is "biomaterial".

A biomaterial is a synthetic material used to replace part of a living system or to function in intimate contact with living tissue (Ratner et al, 1996). The Clemson University Advisory Board for Biomaterials defined a biomaterial as "a systemically and pharmacologically inert substance designed for implantation within or incorporation with living systems". In 1986, the Consensus Conference of the European Society for Biomaterials defined a biomaterial as "a nonviable material used in a medical device, intended to interact with biological systems" (Williams, 1987a). Another definition of biomaterial is "any substance (other than drugs) or combination of substances synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ, or function of the body" (Hulbert et al, 1987; Helmus and Tweden, 1995). A biomaterial is different from a biological material such as bone which is produced by a biological system.

The really significant part of the Consensus Conference definition is that it has referred to the interaction with biological systems. To qualify for this descriptive definition, a material must be used in a situation in which it is to remain in contact with living systems for a sufficiently long time for some significant interaction to take place. These situations largely involve implantation in the body but can also be extracorporeal circuits (e.g, kidney machines) and devices having intentionally prolonged contact with external surfaces (e.g, contact lenses and wound dressings). To date, biomaterials are used clinically or experimentally in implantable electronic devices, drug delivery systems, hybrid artificial organs, bone substitutes, ligament and tendon replacements, extracorporeal blood separation columns, and so on.

此为试读,需要完整PDF请访问: www.ertongbook.com

in Wang

The UK Office of Science and Technology (OST) in 1995 identified biomaterials as one of the eight priority areas within the sector of materials: i .e . a new generation of materials which encourage and enhance the restoration and repair of body tissue function (UK OST Report, 1995) .“ Biomaterials save lives, relieve suffering and improve the quality of life for a large number of patients every year ” (IoM Report, 1995) . In order to develop and use materials in medicine, one must have sufficient knowledge of different disciplines and collaborate with people of various specialties . Knowledge in the following three areas is essential:

(1) Materials science and engineering: processing - structure - property interrelationship of synthetic and biological materials, including metals, ceramics, polymers, composites, tissues, etc . .

(2) Biology and physiology: cell and molecular biology, anatomy, animal and human physiology, etc . .

(3) Clinical sciences: dentistry, ophthalmology, orthopedics, plastic and reconstructive surgery, cardiovascular surgery, neurosurgery, immunology, histopathology, experimental surgery, veterinary medicine and surgery, etc . .

The role of biomaterials has been influenced considerably by advances in many areas of science and technology . Biomaterials can be classified in a number of ways according to different criteria (Black, 1992; Greco, 1994; Park and Lakes, 1992) . The classification of biomaterials as polymers, metals, ceramics, and composites, as shown in Table 1. 1, is generally adopted .

Table 1 .1 Materials for use in the body

Material	Advantage	Disadvantage	Application
Polymers			
Nylon PTFE Polyester Silicone	Ductile, light, easy to fabricate	Not strong, prone to creep, degradable	Suture, vascular prosthesis, accetabular cup, artificial ligament
Metals			
Ti and its alloys Co - Cr alloys Stainless steels Au, Ag, Pt	Ductile, strong, tough	Prone to corrosion, unwanted ion release	Artificial joint, bone plate and screw, dental root implant, pacer, suture wire
Ceramics			
Carbon Aluminum oxide Hydroxyapatite	Biocompatible, Inert or bioactive, strong in compression, stiff	Brittle, weak in tension, sometimes fragile	Cardiovascular device, dental prosthesis, joint prosthesis, orthopedic implant

Composites			
Carbon-carbon Metal - PMMA HA - HDPE	Strong, stiff, tailor-made, distinctive properties	Difficult to make, high production cost	Joint implant, heart valve, bone cement

in Wang

According to Hench and Ethridge, "a bioactive material is one that elicits a specific biological response at the interface of the material which results in the formation of a bond between the tissues and the material" (Hench and Ethridge, 1982). At present, bioactive materials include some calcium phosphate compounds, bioactive glasses, bioactive glass-ceramics, bioactive ceramic coatings deposited on metal substrates, composites containing bioactive ceramic phase(s), etc. A characteristic feature common to these materials is that they bond to human bone with no fibrous tissue at the interface.

1.2 Calcium Phosphate Ceramics

Calcium phosphate bioceramics have been in use in medicine and dentistry for more than 20 years. The interest in one group member, hydroxyapatite, arises from its similarity to bone apatite, the major component of the inorganic phase of bone, which plays a key role in the calcification and resorption processes of bone (Fawcett, 1986). In the mid-1970s, three groups, Jarcho et al. in the USA, de Groot et al. in Europe, and Aoki et al. in Japan, simultaneously but independently worked toward the development and commercialiation of hydroxyapatite as a biomaterial for bone repair, augmentation, and substitution.

Different phases of calcium phosphate ceramics can be used in medicine, depending on whether a bioactive or a resorbable material is desired. Table 1.2 lists calcium phosphates that are often encountered in research and clinical in use.

Table 1.2 Family of calcium phosphate compounds

Mineral Name	Chemical Name	Chemical Formula	Ca:P (Molar Ratio)
Monetite	Dicalcium phosphate (DCP)	$CaHPO_4$	1.00
Brushite	Dicalcium phosphate dihydrate (DCPD)	$CaHPO_4 \cdot 2H_2O$	1.00
	Octocalcium phosphate (OCP)	$Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O$	1.33
Whitlockite		$Ca_{10}(HPO_4)(PO_4)_6$	1.43
	Tricalcium phosphate (TCP)	$Ca_3(PO_4)_2$	1.50
Hydroxyapatite	Hydroxyapatite (HA)	$Ca_{10}(PO_4)_6(OH)_2$	1.67
Hillinstockite	Tetracalcium phosphate (TTCP)	$Ca_4P_2O_9$	2.00

The stable phases of calcium phosphate ceramics depend considerably on the temperature and the presence of water, either during materials processing or in the in-service environment. At body temperature, only two calcium phosphates are stable when in contact with aqueous media such as body fluids. At pH < 4.2, the stable phase is $CaHPO_4 \cdot 2H_2O$ (brushite), while at pH > 4.2, the stable phase is $Ca_{10}(PO_4)_6(OH)_2$

(hydroxyapatite). t higher temperatures, other phases such as $Ca_3(PO_4)_2$ (TCP) and $Ca_4P_2O_9$ (TTCP) are present. The unhydrated high-temperature calcium phosphate phases interact with water or body fluids at 37℃ to form hydroxyapatite (HA).

1.2.1 Biological Apatites

Biological apatites constitute the mineral phase of calcified tissues such as bone, dentine, and enamel in the body and also some pathological calcifications. They are similar to synthetic HA, but they differ from HA in composition, stoichiometry, and physical and mechanical properties. Biological apatites are usually calcium-deficient as a result of various substitutions at regular HA lattice points. It is therefore not appropriate to simply refer to biological apatite as hydroxyapatite.

1.2.1.1 Composition and Structure

The general chemical formula for biological apatites is

$$(Ca, M)_{10}(PO_4, CO_3, Y)_6(OH, F, Cl)_2 \qquad (1.1)$$

where M represents metallic elements such as Na, K, and Mg; and Y represents functional groups such as acid phosphate, sulfates, etc. As compared to synthetic HA with the chemical formula of $Ca_{10}(PO_4)_6(OH)_2$, substitution in biological apatites by the carbonate group for the phosphate group takes place in a coupled manner, i.e. CO_3 for PO_4 and Na for Ca. The coupled substitution is necessary to balance charges for the substitution. Differences in composition among apatites in human enamel and bone and HA are shown in Table 1.3.

Table 1.3 Composition of biological apatites and hydroxyapatite

Major Constituent	Biological Apatite		Hydroxyapatite (wt%)
	In enamel (wt%)	In bone (wt%)	
Ca	36.00	24.50	39.60
P	17.70	11.50	18.50
Na	0.50	0.70	
K	0.08	0.03	
Mg	0.44	0.55	
F	0.01	0.02	
Cl	0.30	0.10	
CO_3^{2-}	3.20	5.80	
Trace elements: Sr, Pb, Ba, Fe, Zn, Cu, etc.			

此为试读,需要完整PDF请访问: www.ertongbook.com

in Wang

Ca :P (molar ratio)	1 .62	1 .65	1 .67

1 .2 .1 .2 Property

Because of substitutions and hence differences in composition, biological apatites possess different physical and mechanical properties, compared to synthetic HA . Table 1 .4 lists the properties of apatites in human enamel and bone and HA .

Table 1 .4 Properties of biological apatites and hydroxyapatite

Property	Biological Apatite		Hydroxyapatite
	In enamel	In bone	
Lattice parameter / nm			
a	0 .9441	0 .9419	0 .9422
c	0 .6882	0 .6880	0 .6880
Crystal size / nm	130 × 30	25 × (2 .5 - 5 .0)	in micrometers
Elastic modulus / GPa	14	7 - 30	10
Tensile strength / MPa	70	50 - 150	～100

The biological apatite of enamel differs from those of dentine and bone in crystallinity and in the concentration of minor elements . It has the largest apatite crystal size compared to dentine and bone apatites and it is the hardest tissue in the human body . Enamel apatite is less soluble than dentine or bone apatite but is much more soluble than dense HA . X-ray diffraction (XRD) patterns and infrared (IR) spectra of biological apatites (in bone, enamel, and dentine) are distinctively different from those obtained from synthetic HA .

Sintering products of biological apatites of enamel, dentine, and bone are different, which indicates the differences in their composition and calcium deficiency (LeGeros, 1990) . Sintering human enamel and dentine apatites above 800℃ yielded hydroxyapatite and small amounts of β-tricalcium phosphate (β-TCP) . Sintering human bone apatite above 800℃ gave hydroxyapatite (HA) and minor amounts of CaO . Sintering animal bones resulted in the formation of β-TCP or CaO depending on the age and species of animal (LeGeros, 1991) .

1 .2 .2 Hydroxyapatite

Hydroxyapatite belongs to the apatite family . Apatite is the name given to

a group of crystals of the general chemical formula $M_{10}(RO_4)X_2$, where R is most commonly phosphorus, M could be one of several metals, although it is usually calcium, and X is commonly hydroxide or a halogen such as fluorine or chlorine. Possible M, R and X are listed below (Aoki, 1994):

M = Ca, Sr, Ba, Cd, Pb, Mg, Na, K, etc.
R = P, CO_3, V, As, S, Si, Ge, Cr, B, etc.
X = OH, CO_3, O, BO_2, F, Cl, Br, vacancy, etc.

The mineral, first called apatite in 1788 by Werner, had been confused earlier with other minerals such as aquamarine, olivine, and fluorite (Deer et al, 1985). Apatite minerals are found in almost all igneous rocks as well as in sedimentary and metamorphic rocks.

1.2.2.1 Structure

Hydroxyapatite is the most commonly used calcium phosphate in the medical field, as it possesses excellent biocompatibility and is osteoconductive. It has the chemical formula $Ca_{10}(PO_4)_6(OH)_2$ and a Ca/P molar ratio of 1.67. Its theoretical density is 3.156 g/cm^3. HA crystal has hexagonal rhombic prisms, with the space group being $P6_3/m$. This space group is characterized by a sixfold *c*-axis perpendicular to three equivalent *a*-axes (a_1, a_2, and a_3) at angles of 120° to each other. Its unit cell contains a complete representation of the apatite crystal, consisting of Ca^{2+}, PO_4^{3-}, and OH^- groups. The 3-D crystal structure of HA is shown in Fig. 1.1 (Aoki, 1994). The structure of HA projected on the *c* axis onto the basal plane is shown in Fig. 1.2 (Aoki, 1994). The hydroxyl ions lie at the corners of the projected basal plane and occur at equidistant intervals (0.344 nm) along the columns perpendicular to the basal plane and parallel to the *c*-axis. Six of the 10 calcium ions in the unit cell are associated with the HA in these columns, resulting in strong interactions among them.

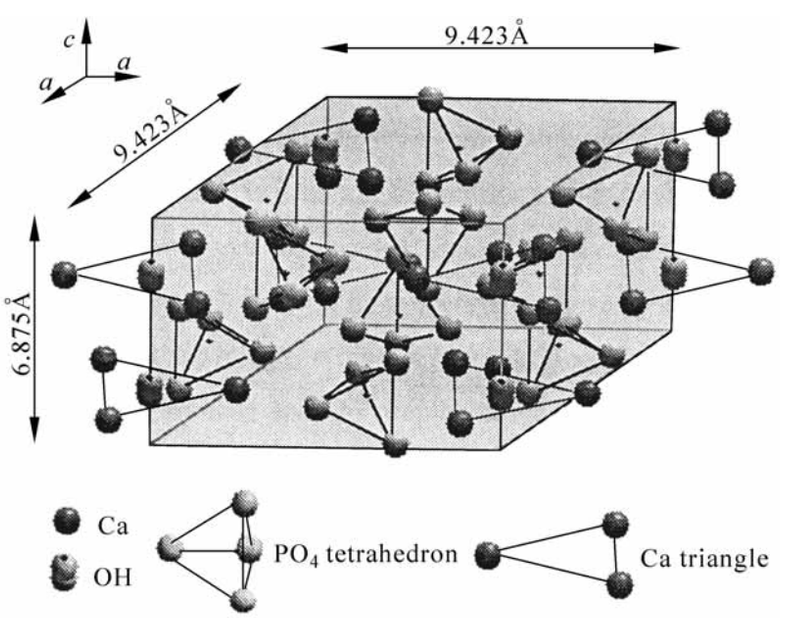

Figure 1.1 Crystal structure of hydroxyapatite

in Wang

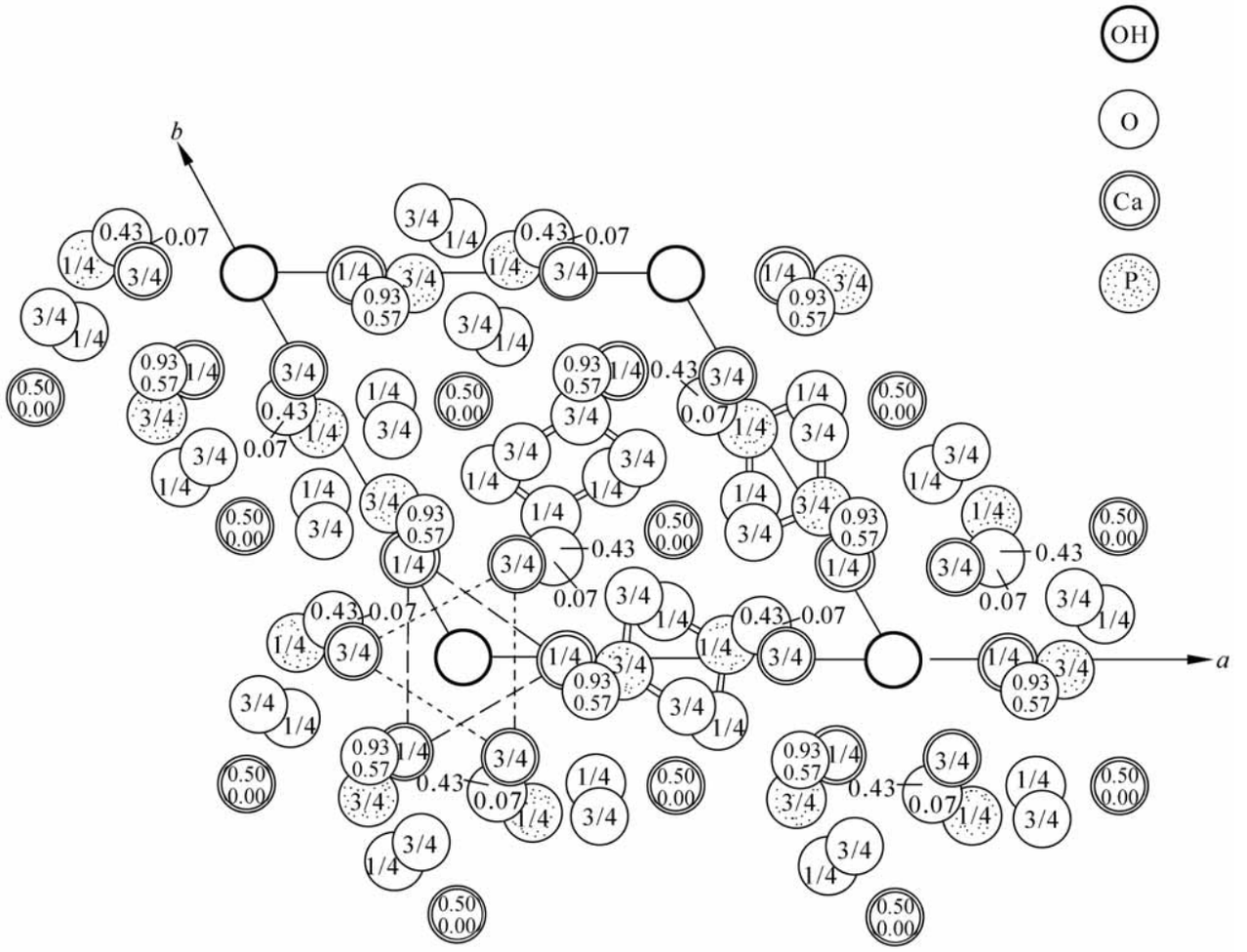

Figure 1. 2 Structure of hydroxyapatite projected onto the basal plane

The crystallographic data of HA are summarized below:

Crystal system:	exagonal
Space group:	P6$_3$/ *m*
Lattice constants:	*a* = 0 .9432 nm, *c* = 0 .6881 nm
Chemical unit number:	*Z* = 1
Molecular weight:	*M* = 1004 .8

Substituted apatites such as $Ca_{10}(PO_4)_6F_2$ and $Ca_{10}(PO_4)_6Cl_2$ have similar structures, with F and Cl substituting of OH in its position .

The apatite structure is very hospitable in allowing the substitutions of many other ions . Ca, PO_4, and OH groups in apatite can be substituted . Carbonate (CO_3) can substitute either for the hydroxyl (OH) or the phosphate (PO_4) group, designated as Type A or Type B substitution, respectively . The substitutions cause morphological changes in precipitated apatite crystals as well as their properties . For example, CO_3 substituted apatite is more soluble than CO_3-free synthetic apatite .

1 .2 .2 .2 Powder Synthesis

Hydroxyapatite in the particulate form can be produced by using a variety of methods . he characteristics of HA powders have significant effects on the subsequent products with HA being in the form of a dense or porous structure, in coatings, or in composites .

Wet Method

The wet method can be used for the mass production of crystalline HA or noncrystalline calcium phosphate powder . There are typically two types of process in the wet method: one involves the neutral reaction of acid and alkaline solutions; the other involves the reaction of calcium salts and phosphate salts . The chemical reactions are shown below:

$$\text{(i)}\quad 10Ca(OH)_2 + 6H_3PO_4 \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 18H_2O \qquad (1.2)$$

$$\text{(ii)}\quad 10CaCl_2 + 6Na_2HPO_4 + 2H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 12NaCl + 8HCl \qquad (1.3)$$

$$10Ca(NO_3)_2 + 6(NH_4)_2HPO_4 + 2H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 12NH_4NO_3 + 8HNO_3 \qquad (1.4)$$

The first synthetic HA powder was prepared by using the method developed by Tagai and Aoki (Tagai and Aoki, 1978) . Production involved preparing a 200 ml suspension of $Ca(OH)_2$ and slowly adding 200 ml of 0 .28 M H_3PO_4 . The solution was maintained at a temperature of (50 ± 1) ℃ and agitated with a magnetic stirrer for the duration of the addition process and for a subsequent 24 h after acid addition had ceased . The

resulting precipitate was allowed to settle for a period of days, and some of the water was permitted to evaporate . After this, the powder was dried in an oven at 110℃ .

Dry Method

The dry method is utilized to prepare crystalline HA by employing a solid-state reaction . For example, when brushite, $CaHPO \cdot 2H_2O$, and calcium carbonate are used as starting materials for the preparation of HA, the following continuous reaction occurs (> 900℃):

$$6CaHPO \cdot 2H_2O + 4CaCO_3 \quad Ca_{10}(PO_4)_6(OH)_2 + 4CO_2 + 14H_2O \qquad (1.5)$$

HA synthesized by the dry method is very fine, and the crystallinity is excellent .

Hydrothermal Method

As mentioned above, HA prepared by the wet method in atmosphere consists of very small crystals with lattice defects . In order to obtain large, perfect, single crystals of HA, it is preferable to use the hydrothermal technique . Peroff and associates succeeded in growing an HA crystal to 0.3 mm under hydrothermal conditions of 300℃ and about 85 kg/ cm^2, Mengeot and associates synthesized an HA single crystal of 7 mm×3 mm×3 mm, and Eyses and associates synthesized an 8 mm crystal (Aoki, 1994) . The lattice constants of HA prepared by the hydrothermal method depend on the reaction temperature and pressure .

1.2.2.3 Manufacture of Dense Hydroxyapatite

HA can be prepared in a dense or macroporous object with pores being as large as 500 μm . Dense HA is described as having a maximum microporosity of 5% by volume with the micropores measuring about 1 μm in diameter and consisting of crystals with size exceeding 200 nm . Dense HA is generally sintered under specific conditions . Density up to 95% of the theoretical value is achievable . A flow chart of the fabrication process of dense HA by pressureless sintering, hot pressing, and hot isostatic pressing techniques is shown in Fig.1.3 .

Green Body Formation

This is the first step in producing dense HA stock or products . It involves forming HA powders into desired shapes . The precursor in the production of

ceramic components is a low density and particulate (green) compact . This green compact is generally of low strength since particles are held together only by frictional/ mechanical interlocking and low energy bonds such as van der Waals forces .

The primary goal of every compacting technique is to obtain homogeneity in all aspects, combined with the secondary goal of sufficiently high density of the green body . A variety of compacting techniques are used since the advantages and disadvantages differ per technique . They are divided into essentially dry consolidation (pressing), consolidation with doughs (injection molding or extrusion), and consolidation with slips (slip or tape casting) . In pressing, there are two techniques that can be used: die pressing and isostatic pressing . Using die pressing, a certain amount of powder is put into a die and shaped by punches under a load . Since in this method the load is applied uniaxially, the method is also called (pseudo-) uniaxial pressing . Uniaxial pressing is the common method for compacting powders . During isostatic pressing, a powder batch is consolidated by isostatic pressure applied by a fluid on a reshaped compact protected with an impermeable cover . Technical details of isostatic pressing are given by James (James, 1983) . The basic concept behind injection molding of ceramic parts is to put the numerous possibilities available in plastics technology to good use in ceramics . In ceramic processing, a thermoplastic material is mixed with ceramic powder . The process consists essentially of three steps: first, the filling of a relatively cold mold with the hot melt of the feedstock, i . e , a thermoplastic material mixed with the ceramic powder . Secondly, cooling and solidification of the melt, and, third, ejection of the formed product . After the injection molding process, the organic part has to be removed, usually, by burn-out . Details of ceramic powder injection molding are discussed elsewhere (German, 1990) . For slip casting, various modifications exist . In all casting techniques, the use is made of a slip that is poured into a porous mold through which the solvent is removed either by capillary or by external pressure . Fairly complicated shapes can be produced (by using multipart molds) at relatively low cost, but the production speed is low .

Viscous plastic processing (VPP) has been in use for producing high-strength ceramics and was recently investigated for dense HA (Shaw et al . , 1995) . VPP operates by incorporating a high rate mixing step to break down agglomerates and simultaneously form a monolayer of polymer over each particle to reduce reagglomeration . This homogenization of the starting powder effectively removes potential crack initiation sites . Thus, the strength of ceramics processed through VPP is improved over those processed through conventional techniques such as pressing or slip casting . During VPP, the HA powder is loosely mixed with an organic binder and solvent to produce a crumb-like green mixture . This green mixture is then

此为试读,需要完整PDF请访问: www.ertongbook.com