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Biodegradable Polymer-Based Scaffolds for Bone Tissue Engineering

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Preface

In order to overcome the problems of current transplantation therapy, tissue engineering emerged to provide an alternative solution. Being an interdisciplinary and multidisciplinary field, tissue engineering aims to recreate tissues and organs which can provide biologically similar functions. Scaffolds play a pivotal role in tissue engineering. Scaffolds function as temporary extracellular matrices for cell accommodation, proliferation, and differentiation. They serve as three-dimensional templates for neotissue formation.

This book is anticipated to address the principles, methods, and applications of biodegradable polymer-based scaffolds for bone tissue engineering. The general principle of bone tissue engineering was reviewed and the traditional and novel scaffolding materials, their properties, and scaffold fabrication techniques were explored. One of the promising technique to fabricate scaffolds, the freeze-drying technique, was investigated for fabricating polymer and composite scaffolds based on poly(hydroxybutyrate-co-hydroxyvalerate) (PHBV) polymers. The scaffolds were evaluated using various techniques. This book is part of the Ph.D. thesis submitted to the University of Hong Kong. This book not only provided the comprehensive summary of the current trends in scaffolding design but also provides the new trends and directions for scaffold development for the ever expanding tissue engineering applications.

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Contents

Notations

Variable	Explanation
ALP	Alkaline phosphatase
BG	Bioactive glass
cm	Centimeter
COOH	Carboxyl end group
D	Diffusion coefficient
D_o	Temperature-independent constant/pre-exponential
E	Young's modulus, Ester
ECM	Extracellular matrix
FDA	Food and drug administration
g	Gram
h	Hour
HA	Hydroxyapatite
HB	Hydroxybutyrate
HV	Hydroxyvalerate
H_2O	Water
J	Joule
K, K'	Rate constant
K	Kelvin
MSC	Mesenchymal stem cells
ml	Milliliter
mm	Millimeter
MPa	Megapascal
M_{nt}	Molecular weight after in vitro degradation at time t
M_n	Number average molecular weight at time t
M_{no}	Initial number average molecular weight
NG	Nucleation and growth
PBS	Phosphate buffered saline
PCL	Poly(ε-caprolactone)
PDLA	Poly(D-lactide)
PET	Poly(ethylene terephthalate)
PGA	Poly(glycolic acid)

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Variable	Explanation
PHB	Poly(hydroxybutyrate)
PHBHHx	Poly(hydroxybutyrate-co-hydroxyhexanoate)
PHBV	Poly(hydroxybutyrate-co-hydroxyvalerate)
PLA	Poly(lactic acid)
PLGA	Poly(lactic acid-co-glycolic acid)
Q	Activation energy for diffusion
R	Gas constant
rpm	Rotational per minute
SD	Spinodal decomposition
SEM	Scanning electron microscopy
SLS	Static light scattering
t	Degradation time
T	Absolute temperature
TCP	Tricalcium phosphate
TE	Tissue engineering
TIPS	Thermally induced phase separation
W_i, W_d	Specimen weights before soaking in PBS
W_f, W_w	Specimen weights after soaking in PBS
wt	Weight
%	Percentage
σ	Tensile strength
ε	Elongation at fracture
º	Degree
°C	Degree Celsius
β-TCP	β-Tricalcium phosphate
3D	Three dimensional

Chapter 1
Scaffolds for Tissue Engineering

Abstract The aim of tissue engineering is to develop cell, construct, and living system technologies to restore the structures and functions of damaged or degenerated tissues. Surgical strategies that have evolved to deal with tissue loss include organ transplantation from one individual to another, tissue transfer from a healthy site to an affected site in the same individual, and replacement of tissue functions with synthetic material devices. All of these strategies have limitations. Organ transplantation is not always feasible as the number of organ donors is far less than the number of patients waiting for organ transplantation. The complications of immuno-suppressive agents are also trouble for the organ recipients. Tissue engineering (TE) seeks to provide a new solution to tissue loss. Scaffolds with porous microstructures are commonly used in TE. This chapter reviews and reports the TE strategy, requirements of scaffolds in TE, as well as different biomaterials that are often used to fabricate tissue engineering scaffolds.

Keywords Bone tissue engineering • Scaffolds • Bone structure • Biomaterials for scaffolds

1.1 Tissue Engineering

The definition of tissue engineering is "the application of principles and methods of engineering and the life sciences toward fundamental understanding of structure–function relationships in normal and pathological mammalian tissue and the development of biological substitutes that restore, maintain, or improve tissue function" (Bell 1993). In terms of its goals, tissue engineering can be considered as following: (1) providing cellular prostheses or replacement parts for the human body; (2) providing acellular replacement parts capable of inducing regeneration; (3) providing tissue or organ-like model systems populated with cells for basic research and for many applied uses such as the study of disease states using aberrant cells; (4) providing vehicles for delivering engineered cells to the organism, and (5) providing surfacing non-biological devices (Bell 1993).

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The tissue construct in tissue engineering is classified into two major types, closed systems and open systems (Langer and Vacanti 1993). The implant which is used as external organ support is termed as the closed system whereas the scaffold with attached cells implanted into the body is termed as open system. The scaffold is three-dimensional (3D), highly porous with an interconnected pore network which provides as a intermediary template/model for tissue regeneration. In the general procedure of tissue engineering, the cells can be isolated from the biopsy taken from the patient, expanded in vitro, and seeded into a scaffold (Schultz et al. 2000). Incorporated with signalling molecules in some strategies, this cell-scaffold construct can be cultured in the bioreactor until an appropriate and developed graft is formed. This final 3D cell-scaffold construct can be implanted into the patient (Temenoff and Mikos 2000). It has been demonstrated that bone has the highest possibility for regeneration among many other tissues in the body (Chen et al. 2006).

1.2 Replacement and Regeneration of Bones

1.2.1 Bone Structure and Composition

At the ultra-structural level, bone is a composite with mechanical properties which can be matched by man-made composites (Wang 2004). In order to develop bone replacement materials, bone serves as the template. Human body is supported by bones which are the substantial unit of human skeletal system. As a natural tissue, bone has a complex structure where several macroscopic to microscopic levels of organization can be identified (Park 1979). Bone possesses an intricate structure. The basic unit of bone is the Haversian system (also known as “osteons”), which is a hollow, laminated rod of collagen and calcium phosphate. The hollow core is a nutrient channel, the Haversian canal. Many of these Haversian systems within the shaft of a long bone are bundled together in parallel and form a kind of bone called cortical or compact bone, which is optimized to handle mechanical forces. Near the ends of the bones, where the stresses become more complex, the Haversian systems play out and branch to form a meshwork of cancellous, or spongy bone.

Human bone contains the mineral crystallites which are structurally calcium-deficient, carbonate-substituted hydroxyapatite which are generally referred to as bone apaptite. The normal dimension of bone apatite is $5 \times 5 \times 50$ nm with a rod-like (or sometimes plate-like) microstructure and is embedded in collagen fibers. Bone apatite occupies about 50 % of the total volume in mature bone. The particular microstructural organization of bone is a function of age and it varies between different bones and between different locations of the same bone (Wang 2004).

Two levels of composite structures are considered when developing bone substitutes. First of which is the bone apatite reinforced collagen forming individual lamella (nanometer to micrometer scale) and secondly the osteon reinforced interstitial bone (on the micrometer to millimeter scale). The apatite-collagen composite at the microscopic level provides the basis for producing bioceramic-polymer composites for bone replacement.

1.2.2 Mechanical Properties of Bone

By assessing whole bones in vivo, the mechanical behavior of bones can be investigated. The mechanical properties of cortical or cancellous bones are determined in vitro using standard or miniature specimens that match up to various standards originally designed for testing conventional materials such as metals and plastics (Wang 2004). It is very important to maintain the water content of bone for mechanical assessment as the behavior of bone in the "wet" condition can be significantly different from that bone in a "dry" condition (Fung 1993). Cortical bone has a range of associated properties rather than a unique set of values (Table 1.1) with respect to orientation, location and age (Wang 2004).

The mechanical behavior of bone can be explained using a simple composite model by treating bone as a nanometer-scale composite (Fig. 1.1). In bone, brittle apatite acts as a stiffening phase whereas ductile collagen provides a tough matrix. Therefore the tensile behavior of bone reveals the combinational effect of these two major constituents. A good understanding of the structure and properties of bone yields a good insight into the structural features of bones as well as provides the property range for approximating mechanical compatibility that is required of a bone analogue material for structural replacement with a stabilized bone-implant interface (Wang 2004). It is also important to take into account that, bone can alter its properties and configuration in response to changes in mechanical demand which is unlike any engineering material.

Table 1.1 Mechanical properties of bone and current implant materials (Wang 2004)

Material	E (GPA)	σ (MPa)	ε (%)
Cortical bone	7–30	50–150	1–3
Cancellous bone	0.05–0.5	10–20	5–7
Co-Cr alloys	230	900–1540	10–30
Stainless steel	200	540–1000	6–70
Ti-6Al-4 V	106	900	12.5
Alumina	400	450	~0.5
Hydroxyapatite	30–100	60–190	
Polyethylene	1	30	>300

E Young's modulus, σ tensile strength (flexural strength for alumina), ε elongation at fracture

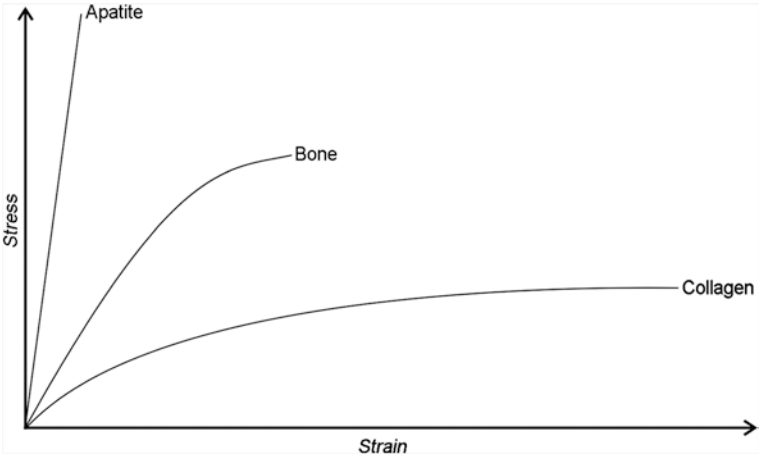

Fig. 1.1 Schematic diagram showing the mechanical behavior of *apatite*, *collagen*, and compact *bone*

The structure and properties of cancellous (or spongy) bone is well documented (Gibson and Ashby 1997). The cancellous bone is made up of an interconnected network of rods or plates. Low density, open cells are produced by a network of rods while closed cells are produced when the rods progressively spread and flatten as the density increases. The relative density of cancellous bone varies from 0.05 to 0.7. The compressive stress–strain curve of cancellous bone possesses the characteristics of a cellular solid. Under compression, the scaffolds exhibited linear elasticity at low stresses followed by a long plateau of cell wall collapse and then a regime of densification in which the stress rose steeply.

The linear elasticity is controlled by cell wall bending, the plateau is associated with collapse of the cells (of the "cellular structure") and when the cells have almost completely collapsed, opposing cell walls touch, with further strain compressing the solid itself, giving the final region of rapidly increasing stress (Gibson and Ashby 1997). As the relative density increases, the cell walls thicken and the pore space shrinks. Increasing the relative density of the scaffold increases the compressive modulus, raises the plateau stress and reduces the strain at which densification starts.

1.2.3 Existing Approaches for Bone Replacement and Regeneration

The requirement for bone is a major clinical and socioeconomic need. It has been reported that the treatment of bone fracture costs over £900 million annually in the UK (Rose and Oreffo 2002). The conventional reconstruction for

bone defects are autologous bone grafts, autogenous bone grafts or alternatively metals and ceramics. If the bone is taken from another part of the patient's own body, it is referred as autologous bone grafts. For bone healing and regeneration, autologous bone provides osteogenic cells and essential osteoinductive factors (Rose and Oreffo 2002). It also imparts relatively better chance of success. Nevertheless, the limitations of autograft tissues are that the availability of this type of tissues are inadequate for the required applications (Rose and Oreffo 2002).

Allografts which refer to tissues taken from some other's body, may introduce the risks of immunological rejection problem and of transmission of pathogens from donor to host (Spitzer et al. 2002; Yaszemski 2004). Another limitation of allograft is the rate of incorporation of host tissue is commonly lower than that of autograft.

Potential substitutes to bone grafts could be metals and ceramics (Yaszemski 2004). Metals which could offer immediate mechanical support at the defect site but as it exhibits poor overall integration with respect to the host tissue, may also fail due to fatigue loading. Ceramics have the disadvantage of brittleness and have low tensile strength and cannot be applied in the locations such as significant torsion, bending, or shear stress.

1.2.4 Needs for Bone Tissue Engineering

Bone tissue engineering, which is a new strategy, provides a prospective solution to regenerate bone in a reliable, economical and physiologically acceptable manner and has emerged as an alternative to bone-grafting procedures over the past decades in order to overcome the various limitations of current grafting procedures and bone substitute biomaterials (Chen et al. 2006). In order to regenerate bone tissue, there are three key elements: osteogenic progenitor cells, osteoinductive growth factors and osteoconductive scaffolds (Schieker et al. 2006). Scaffolds, which act as temporary substrate, facilitate necessary support for cells to proliferate and to maintain differentiated function of the cells, are major component among various strategies such as cell-based and factor-based strategies. In fact, the applicability and success of bone tissue engineering depends on the performance of the scaffolds.

1.3 Requirements for Scaffolds for Bone Tissue Engineering

It has been mentioned in ASTM F2150-02 (ASTM 2002) that a scaffold is a support, delivery vehicle, or matrix to facilitate the migration, binding, or transport of cells or bioactive molecules that is used to replace, repair, or regenerate

tissues. The use of a scaffold can accelerate the wound healing process as the adult mammal does not spontaneously regenerate tissues (other than noncritical-sized bone defect) that have been lost or removed either due to accident or deliberate excision. The scaffolds, which are artificial matrix, can serve as a temporary guide or template for cell adhesion, growth and function. Not only this, they also synthesize extracellular matrix (ECM) and ultimately generate new tissue. It is also expected that the scaffold should be degraded after the formation of natural tissues/organs in order to facilitate an entirely natural tissue replacement. It was mentioned that the critical-sized bone defects might be healed with the aid of scaffolds together with appropriate cell seeding densities and/or growth factors (Khan et al. 2008). Some attributes must be satisfied in order to regenerate new osseous tissue including (1) biocompatibility: the lack of immunogenic response; (2) osteoconductivity: the porous interconnected structure permitting new cells to attach, proliferate, and migrate through the structure and also allows for the exchange of nutrient-waste as well as new blood vessel penetration; (3) osteoinductivity: having the quality for possessing the necessary proteins and growth factors which can induce the progression of mesenchymal stem cells and other osteoprogenitor cells toward the osteoblast lieage; (4) osteogenecity: the osteoblasts which are present at the site of new bone formation that can produce minerals to calcify the collagen matrix to form the substrate for new bone; (5) osteointegration: the newly formed mineralized tissue must be able to form an intimate bonding with the implant material (Khan et al. 2008). Other design considerations are discussed below.

1.3.1 Surface Properties

Scaffolds with appropriate surface chemistry facilitate cell attachment, proliferation and differentiation. Surface roughness is an important factor that can improve osteoblast functions necessary for enhanced bone tissue engineering applications and variations in cellular behavior have been reported to be based on whether a surface was textured or not (Liu et al. 2006). Studies have shown that within the scope of textured surfaces, variations in cellular behavior can only depend on the size (Khan et al. 2008) of the texture or with certain cellular behaviors elicited by nanoscale modifications on the surface of the material.

1.3.2 Physical Properties

Scaffolds should possess three dimensional, highly interconnected porous network together with appropriate porosity, pore size and pore structure for cell growth and transport of nutrients and metabolic waste (Hutmacher 2000). It was described that together with osteoconductivity, a porous structure is critical to allow

osteoprogenitor cells and osteoblasts to occupy the entire matrix after the implantation (Liu et al. 2006). It was also mentioned that not only porosity, the pore sizes must be of suitable diameter to allow osteoblasts and osteoblast-like cells in order to migrate into the center of the matrix allowing complete healing. Thus the necessity of a pore structure tends to acquire critical design decisions in order to consider the structural integrity of the matrix (Liu et al. 2006).

1.3.3 Mechanical Properties

In fact, bone responds to the presence or absence of physical load. The resorption or formation of bones by body occurs in response to these loads. It has been mentioned that it is important to design a matrix that possess mechanical properties that are similar to the tissue in the immediate surrounding area of the defect (Liu et al. 2006). Around the implant site, an overdesigned matrix can induce bone resorption while an underdesigned matrix may fail as a mechanical support to the skeleton. By material selection, formation of composite structures, the overall porosity of the matrix, the mechanical properties can be varied.

1.3.4 Degradation Properties

In order to match cell/tissue growth in vitro or in vivo, scaffolds should be biodegradable and should possess appropriate degradation rate (Hutmacher 2000; Ma 2004). According to ASTM F1635-04a (ASTM 2004), if a material's degradation is primarily hydrolytic in nature, physiological conditions may be modeled at 37 °C under controlled pH conditions. Throughout the degradation period, various properties can be monitored.

1.3.5 Sterilizability

In order to prevent infection, scaffold materials must be sterilizable (Zhou 2007). The scaffolds should possess minimum residues if chemicals such as ethylene oxide are used to sterilize the samples. Gamma radiation is an accepted alternative to ethylene oxide sterilization. Sterilization methods should be carefully selected so that it can have little effect on the properties of scaffolds. The effects of γ-ray irradiation on PHB and PHBV had been reported by several researchers. It was reported that PHB and PHBV could be sterilized by γ-ray irradiation (Holmes 1982). Some reduction in molecular weight was reported from this sterilization technique. It was reported that PHBV membranes were sterilized by UV irradiation for 30 min which showed satisfactory cell attachment, spreading and growth

(Lucchesi et al. 2008). It was also reported that surface modified PHBV films could be sterilized by ethanol which promoted osteoblast alignment and confinement (Kenar et al. 2008).

1.4 Candidate Biomaterials for Tissue Engineering Scaffolds

1.4.1 Biopolymers

Polymers are long-chain molecules of high molecular weight made up of a number of small repeating units linked together by covalent bonds. There are a wide variety of polymers including natural materials (such as cellulose and collagen) and synthetic materials (such as polyethylene). If biodegradation is desired of implants, biocompatible and biodegradable polymers can be used. These polymers include poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(hydroxybutyrate) (PHB) and its copolymer poly(hydroxybutyrate-co-hydroxyvalerate) (PHBV). While selecting a biodegradable polymer, apart from other required properties, the degradation rate of the material is also very much important to see if it matches with the growth rate of the new tissue (Liu and Ma 2004). Table 1.2 shows some bone regeneration materials and their properties (Seal et al. 2001).

PGA, PLA and their copolymers poly(lactic acid-co-glycolic acid) (PLGA) are a family of linear aliphatic polyesters, which are most frequently used in tissue engineering. By the degradation of hydrolysis of the ester bonds, these polymers degrade. PGA is one of the most widely used scaffolding polymers. PGA degrades rapidly in aqueous solutions or in vivo because of its relatively hydrophilic nature. It loses mechanical integrity between two or four weeks. The most widely used scaffolds made by this polymer are the nonwoven fibrous fabrics. PLA is another widely used polymer for scaffold fabrication. The extra methyl group in the PLA repeating unit (compared with PGA) makes it more hydrophobic which reduces

Table 1.2 Some bone regeneration polymers and their properties (Seal et al. 2001)

Material	Compressive strength (MPa)	Modulus (MPa)	Porous (μm)	Support cell adhesion
PLA	NR	NR	100–500	Yes
PLGA	60 ± 20	0.5 (tensile),	150–710	Yes
Poly(ortho-ester)	4–16	2.4 (Young's)	NR	Yes
PLA/HA	6–9	NR	NR	Yes
PLA/Ca phosphate	NR	NR	100–500	Yes
PLGA/Ca phosphate	NR	5 (Young's) 0.25	100–500	Yes

NR indicates "not reported"

the molecular affinity to water and leads to a slower hydrolysis rate. It takes several months or even years for a PLA scaffold or implant to lose mechanical integrity in vitro or in vivo. To achieve intermediate degradation rates between PGA and PLA, various lactic and glycolic acid ratios are used to synthesize PLGAs. These polymers (PLA, PGA, and PLGAs) are among the few synthetic polymers approved by the US Food and Drug Administration (FDA) for certain human clinical applications (Zeltinger et al. 2001; Sherwood et al. 2002; Koegler and Griffith 2004; Lu et al. 2005).

There are other linear aliphatic polyesters which are also used in tissue engineering research. They are poly(ε-caprolactone) (PCL) (Allen et al. 1998) and poly(hydroxybutyrate) (PHB). It has been suggested that due to the lower rigidity of PCL, it can be more appropriate for cell growth and formation of ECM than PLLA (Zhao et al. 2004). It is also reported that PCL is also able to reduce the stress shielding effect and the strength of PCL is low and not sufficient for load-bearing application (Lowry et al. 1997). PCL degrades at a slower rate than PLA, PGA, and PLGA. This slow degradation process makes PCL less attractive for general tissue engineering applications but more attractive for long term implant and controlled release applications. PHB is made by microorganisms via fermentation and degrades very slowly because of their hydrophobic nature (Holmes 1982). This polymer has already been used to produce composite biomaterials for potential bone tissue repair. Together with high biocompatibility, PHBV polymers have degradation times much longer than other biocompatible polymers, which can allow the PHBV scaffolds to maintain their mechanical integrity until there is sufficient bone growth throughout the implants (Lutton et al. 2001). PHBV polymers have been found as minimal inflammatory in long term studies of subcutaneous implants in mice and rats (Gogolewski et al. 1993). This polymer indicated positive cell attachment and growth (Kumarasuriyar et al. 2005). Table 1.3 shows the actual and possible applications of biodegradable polymers in medicine and Table 1.4 lists synthetic biodegradable polymers currently used or under investigation for medical applications.

Table 1.3 Medical applications of bioadsorbable polymers (Ikada and Tsuji 2000)

Function	Purpose	Examples
Bonding	Suturing	Vascular and intestinal anastomosis
	Fixation	Fracture bone fixation
	Adhesion	Surgical adhesion
Closure	Covering	Wound cover, local hemostasis
	Occlusion	Vascular embolization
Scaffold	Cellular proliferation	Skin and blood vessel reconstruction
	Tissue guide	Nurve reunion
	Drug delivery	Sustained drug release

Table 1.4 Biopolymers currently used or under investigation for biomedical application (Ikada and Tsuji 2000)

Polymers	Structure	Degradation Rate	Biomedical Application
PGA	Crystalline	100 % in 2–3 months	Suture, soft tissue, fracture fixation
PLGA	Amorphous	100 % in 50–100 days	Oral implant, drug delivery
PLA	Semicrystalline	50 % in 1–2 years	Fracture fixation, ligament
PCL	Semicrystalline	50 % in 4 years	Augmentation Implant
Poly (orthoester)	Amorphous	60 % in 50 weeks	Suture, lubricant powder, bone plate

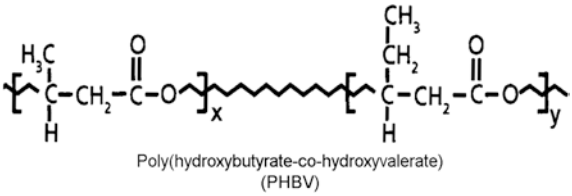

Fig. 1.2 The chemical structure of PHBV (Luzier 1992)

1.4.1.1 Poly(hydroxybutyrate) Polymer and Poly(hydroxybutyrate-co-hydroxyvalerate) Copolymer

Poly(hydroxybutyrate-co-hydroxyvalerate) PHBV copolymers are thermoplastic polyesters. These polymers are composed of hydroxybutyrate (HB) units with between 0 and 24 % of hydroxyvalerate (HV) units appearing randomly throughout the polymer chain (Fig. 1.2) (Luzier 1992).

1.4.1.2 PHB and PHBV Synthesis

PHB and PHBV are produced by fermentation. A wide range of microorganisms can be used to make PHB or PHBV. Among them, the bacterium, *Alcaligenes,* are quite common in the environment and they can grow on a wide range of carbon sources in both aerobic and anaerobic conditions. The strain *Alcaligenes eutrophus* grows very efficiently on glucose and is safely handled in large quantities.

Bacteria need a carbon source, an energy source, nitrogen, phosphorus, sulfur, trace elements, water and oxygen for balanced growth. If one nutrient (e.g., N, P, or S) is limited, bacteria cannot produce amino acids and proteins, and they cannot grow. These facts are exploited by PHBV production (Holmes 1982; Galgut et al. 1991). Polymeric storage materials are usually formed when the microorganisms are exposed to stress conditions and when their environment changes to unsuitable living conditions. That is the lack or shortage of one or more essential nutrients and/or decreased oxygen supply for aerobic species, the microorganisms produce intracellular carbon

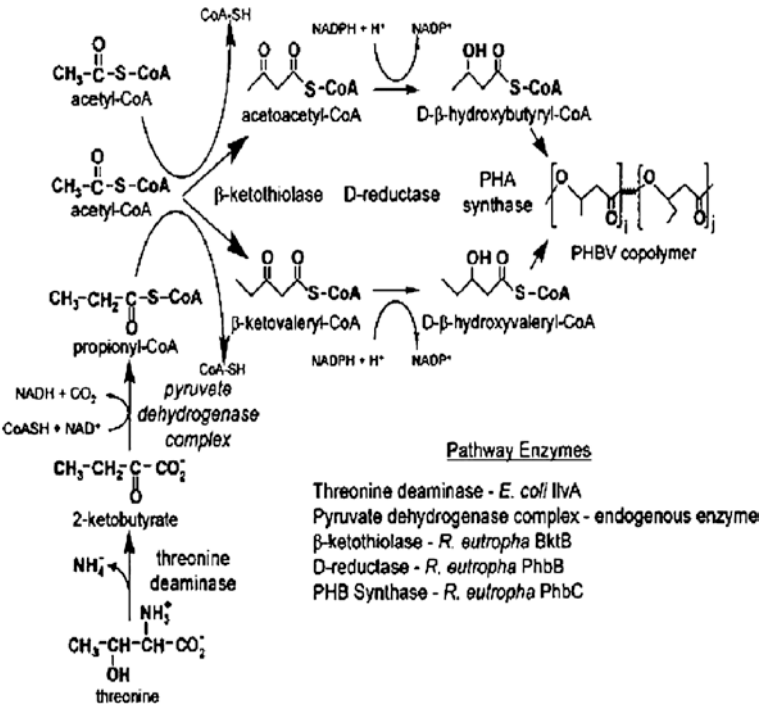

Fig. 1.3 A pathway designed to produce PHBV in the plastids of plants (Slater et al. 1999)

and energy storage in form of polymer granules. Figure 1.3 is the pathway designed to produce PHBV in the plastids of plants.

1.4.1.3 Physical, Mechanical and Miscellaneous Properties of PHB and PHBV

The typical properties of PHBV and the thermal properties and degradation products of PGA, PLLA and PHBV are given in Tables 1.5 and 1.6, respectively.

Table 1.5 Typical properties of PHBV (Luzier 1992)

Property	HV content, mol %		
	0	10	20
Melting point (0 °C)	177	140	130
Crystallinity (%)	80	60	35
Tensile strength (MPa)	40	25	20
Flexural modulus (GPa)	3.5	1.2	0.8
Extension at break (%)	8	20	50
Impact strength (J/m)	60	110	350

Table 1.6 Thermal properties and degradation products of PGA, PLLA and PHB (Holmes 1982; Galgut et al. 1991)

Polymer	T_m (°C)	T_g (°C)	Degradation products
PGA	225–230	35–40	Glycolic acid
PLLA	173–178	60–65	L-lactic acid
PHB	175	4	3-Hydroxybutanoic acid

Another interesting property of the PHB polymer is that they exhibit piezoelectric properties. This phenomenon has physiological significance in the stimulation of bone growth. PHB behaves similarly as poly(γ-methyl-L-glutamate) in that the piezoelectric response is generated by the application of a shear stress to orientate polymer crystallites (Holmes 1982).

1.4.1.4 Biodegradation of PHB and its Copolymers

It has been reported that, PHB is biodegradable in vivo as a subcutaneous or intramuscular implant (Holmes 1982). The ultimate biodegradation product is (R) 3-hydroxybutanoic acid which is a normal metabolite in human blood (Holmes 1982). The polymer itself exhibits good biocompatibility with no cytotoxic response. PHB and its copolymers also hydrolyzed in water with the normal universal acid–base catalysis for esters. At high pH, the rate of degradation is quite fast but the hydrolysis proceeds very slowly in neutral buffer at body temperature. The kinetics does not appear to follow first-order behavior as the reciprocal molecular weight does not decrease linearly with time (Holmes 1982). The plot of the logarithm of molecular weight versus time has been found to be nearly linear. Moreover, the initial experiments suggested that the rate of degradation of PHB in vivo is significantly faster than the in vitro hydrolysis rate at the same temperature and pH. Actually the non-specific esterase and lysozyme enzymes secreted by the body's immune system catalyze the process (Holmes 1982). The range of biodeterioration of implanted films can be varied from very fast to a modest but measurable resorption to virtually undetectable weight loss of fiber monofilament over an 18-months period (Holmes 1982).

1.4.2 Inorganic Materials

Certain inorganic compounds have been studied for bone and other mineralized tissue engineering research in addition to the large variety of polymeric (macromolecular) materials. These materials can be categorized as porous bioactive glasses and calcium phosphates. The most frequently used within the calcium phosphates are β-tricalcium phosphate (β-TCP), hydroxyapatite (HA) and its