

Review Article

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Biomedical Applications of Polyhydroxyalkanoates: The Future Polymer

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ABSTRACT

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Polyhydroxyalkanoates (PHA) are polymers, which are produced by microorganisms in the form of granules under unbalanced growth conditions. They are biocompatible, biodegradable and sustainable, which makes it suitable for synthesising biomedical apparatus. Devices such as sutures, orthopaedic devices, cardiovascular implants, implant patches can be prepared using different combinations of this polymer. The polymer and its composites being biodegradable and sustainable can take over the conventional plastics in near future. This article reviews the various aspects of polyhydroxyalkanoates in the field of biomedicine and concludes PHA as the future polymer.

Introduction

Conventional plastics are organic polymers of high molecular mass. They are usually synthetic, however, being lightweight, flexible, stable and highly durable, it is used in numerous packaging applications, constructional materials, baby products and even in the field of medicine. However, plastic is known to cause various health problems, also being non-biodegradable, it negatively affects the soil, groundwater, water table and eventually the ecosystem. After years of research, PHA was introduced. PHA

stands for Polyhydroxyalkanoates. PHA is a family of carbon neutral polymers, obtained from microorganisms. PHA was first discovered in 1926 by Lemogine in *Bacillus megaterium*, in the form of poly (3-hydroxybutyrate)[PHB] (Chen, 2009).

PHA are referred to as green plastics, being environmental friendly, when compared to the conventional plastic under environmental conditions (in vivo). PHA can be synthesized by over 30% of soil inhabiting bacteria. PHA has no harmful, acute and chronic health effects. PHA is a polymer, consisting of 600-

35000 (R) hydroxy fatty acid monomer units, with an alkyl group attached to it. PHA also exist in the form of homopolymer, random copolymer and block polymers, depending on the bacterial species and growth conditions. Out of these monomeric units 150 are identified. Monomers are classified as short, medium and long chain based on the number of carbon atom present. The short chain consists of 5 or less carbon atoms. The medium chain consists of 5-14 carbon atoms and the long chain consists of more than 14 carbon atoms (Table 1). PHA can be synthesized by either chemical means or biological approaches. Biosynthesis of PHA leads to much higher molecular weight compared with that achieved with chemical methods. Identification of PHA monomers have increased tremendously through the creation of GMO's to produce PHA with specialised functional group (from non PHA strains). They are stored as energy storage material by various microorganisms. PHA promotes long term survival of bacteria under nutrient scarce conditions by acting as carbon and energy resource. To date more than 90 genera of both gram positive and gram negative bacteria have been identified as PHA producers under both aerobic and anaerobic conditions. Bacteria stores PHA within cytoplasm as granules, size 0.2- 0.5 micro meter.

There are two groups of bacteria: (i) Bacteria requires limited nutrients (Phosphorous, Nitrogen, Oxygen and Magnesium) and do not accumulate PHA, during growth phase (Table 3). Example: *Pseudomonas oleovorans*, *Pseudomonas putida*. (ii) Bacteria that accumulate PHA during growth phase and do not require any nutrient conditions. Example: *Escherichia coli*. Increase in carbon/nitrogen ratio promotes PHA accumulation while reverse of it is responsible for cell growth. PHA acts as a potential anti HIV drug, anti cancer drug, antibiotics (Chen and Wu, 2005).

Properties

- (A) Biodegradable
- (B) Biocompatible
- (C) Chemically diverse
- (D) Can be manufactured from renewable carbon source
- (E) Recyclable
- (F) No pollution
- (G) Reduce landfill requirement
- (H) Sustainable
- (I) Resistant to moisture
- (J) Insoluble in water
- (K) Resistant to UV
- (L) Resistant to heat
- (M) Resistant to osmotic shock
- (N) Behave as piezoelectric material
- (O) Soluble in chloroform and other chlorinated solvents
- (P) Melting temperature (40°-180°)
(Chen, 2009) (Table 2)

Applications

Cardiovascular: One of the major use of PHA's has been in the development of cardiovascular products.

PHA in drug delivery: Aims at increasing the availability of drugs as well as controlled release of drugs with respect to time and space. Example: PHB and its polymers are used for the preparation of microspheres and nanoparticles to deliver a range of drug PHBV rods and discs are used to deliver antibiotics. Polyhydroxyoctanoate were evaluated as drug electing stents to reduce the possibility of arterial blockage.

PHB - drug conjugates: One problem with PHB drug delivery system is the rapid release of drugs. Conjugation of drug to PHB polymer could increase release time and availability.

PHB or PHBV as implant patches: Treat defects in the gastrointestinal tract (local resection and closure of defect by suture). Implant needs to meet certain criteria:

Should not cause inflammatory response.
Should be biocompatible.
Should support wound healing/tissue regeneration.
Patch should disappear after serving their purpose (Biodegradable).

PHBHHX as bone tissue engineering materials: PHBHHX has the best performance on attachment, proliferation of bone marrow cells.

PHA as biodegradable drug carriers: Biocompatible PHA with controlled degradation rates was described by Martin *et al.*, Required criteria:

Increased porosity.
Exposed surface area.
Degrade within desirable time frame under physiological conditions.

Anti-ageing products: PHA's are humectants, meaning they can retain moisture, and hydrate the skin by gently exfoliating.

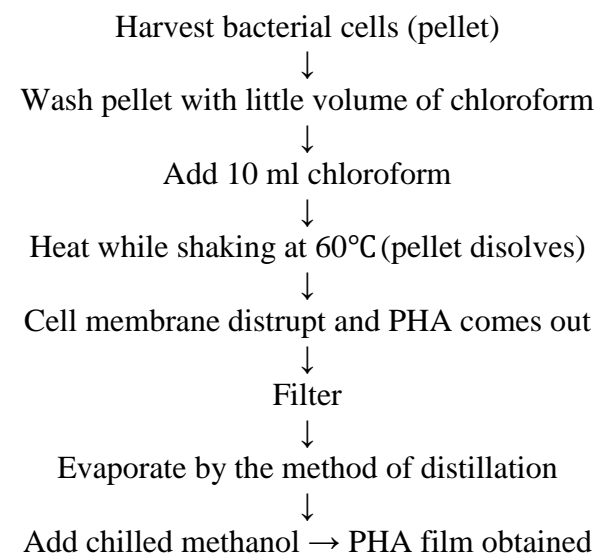
Extraction: Polyhydroxy alkanate are accumulated as granules in the cytoplasm of bacterial cells. Hence, in order to extract PHA, some major requirements are:

Collection and subculturing of bacterial cells on suitable nutrient media
Microscopic observations
Nitrogen estimation

The content and composition of PHA and there polymers are influenced by the strains of microorganisms.

Some of the widely used extraction methods are:

Extraction of PHA from bacteria using chloroform



(Valid for both gram positive and gram negative bacteria with 95% extraction capacity of total PHA)

Extraction of PHA in its natural state

A less drastic method of extraction leaves the PHA in a form similar to that found in bacterial cells. In such a method, bacterial cells are treated with detergents. Detergents degrade the cells thereby releasing PHA and denaturing most other cell components.

The process of purification is completed by a brief treatment with bleach (oxidizing agent), capable of breaking chemical bonds in the polyester, lowering its molecular weight.

(C) Digestion method: This method involves the digestion of the cellular materials surrounding the PHA granules. Chemical methods may be chemical digestion method or enzymatic digestion method.

Table.1

Carbon number	R. Group	Polymer
C4	Methyl	Poly(3-hydroxybutyrate)
C5	Ethyl	Poly(3-hydroxyvalerate)
C6	Propyl	Poly(3-hydroxyhexanoate)
C7	Butyl	Poly(3-hydroxyheptanoate)
C8	Pentyl	Poly(3-hydroxyoctanoate)
C9	Hexyl	Poly(3-hydroxynonanoate)
C10	Heptyl	Poly(3-hydroxydecanoate)
C11	Octyl	Poly(3-hydroxyundecanoate)
C12	Nonyl	Poly(3-hydroxydodecanoate)
C13	Decyl	Poly(3-hydroxytridecanoate)
C14	Undecyl	Poly(3-hydroxytetradecanoate)
C15	Dodecyl	Poly(3-hydroxypentadecanoate)
C16	Tridecyl	Poly(3-hydroxyhexadecanoate)

(Chen, 2009)

Table.2

	Temperature (°)	Density	Crystallinity (%)	Elongation to break (%)
PHB	170-180	1.24	60-80	328
PP	176	-	50	400
PHBV	169.8	1.20	30-80	UPTO 100
P(3HB-co-3HV)	145	-	56	50
PHBHHx	95-150	-	10-50	UPTO 400
P(3HB-co-4HB)	150	-	43	444

Table.3 Types of PHA and the microorganisms from which they are extracted

Microorganisms	Source	Applications	Reference
1. <i>Bacillus megaterium</i>	P(3HB)	Sutures Stents Drug delivery system	(Gouda <i>et al.</i> , 2001)
2. <i>Bacillus cereus</i>	PHB	Drug carrier	(Pradhan <i>et al.</i> , 2018)
3. <i>Alcaligenes eutrophus</i>	PHB-co-PHV	Bone implants	(Ryu <i>et al.</i> , 1997) (Luklinska and Schluckwerder, 2003)
4. <i>Aeromonas caviae</i>	P(3HB-co-3HHx)	Sutures	(Ali and Jamil, 2016)
5. <i>Pseudomonas</i> strain GP4BH1	PHB-co-PHO	Sutures Implant patches	(Muhammadi <i>et al.</i> , 2015)
6. <i>Photobacterium leiognathi</i> + <i>Vibrio harveyi</i>	PHB(major component) + PHV+ HHx(minor component)	Bone implants Sutures	(Boyandin <i>et al.</i> , 2008)
7. <i>Pseudomonas putida</i> KT2442	P(HB-HHx-HO)	Implant patches Sutures	(Ouyang <i>et al.</i> , 2007)
8. <i>Alcaligenes latus</i> DSM1124	P(3HB)	Drug delivery systems	(Yu <i>et al.</i> , 1999)
9. <i>Burkholderia sp.</i> USM(JCM 15050)	P(3HB) based monomer Poly-3-hydroxy-4-methylvalerate	Medical implants Dental materials	(Lau <i>et al.</i> , 2010)
10. <i>Comamonas testosteroni</i>	MCL-PHA	Wound dressing	(Thakor <i>et al.</i> , 2005)
11. <i>Cupriavidus necator</i>	P(3HB)	sutures	(Agustín Martínez <i>et al.</i> , 2015)
12. <i>Cupriavidus necator</i> H16	P(3HB-co-3HV)	Wound management	(Ng <i>et al.</i> , 2010)
13. <i>Cupriavidus necator</i> DSM 545	P(3HB)	Wound management	(Berezina, 2013)
14. <i>Pseudomonas aeruginosa</i> IFO3924	MCL-PHA	Wound dressing and management	(Hori <i>et al.</i> , 2002)
15. <i>Pseudomonas aeruginosa</i> N ^o B 40045	MCL-PHA	Wound dressing	(Fernández <i>et al.</i> , 2005)
16. <i>Thermus thermophilus</i> HB8	P(3HV-co-3HHp-co-3HN-co-3HV)	Sutures Stents	(Pantazaki <i>et al.</i> , 2009)

Table.4

Year	Name of Scientist	Type of Device	Problems
1895	Lane	Metal Plates	Corrosion
1909	Lambotte	Round and tapered metal plate	Corrosion and insufficient strength
1912	Sherman	Metal plates	Corrosion and insufficient strength
1948	Egger	Metal plate held by screws	Unstable and structurally weak
1949	Danis	Compression metal plate (coapteur)	Corrosion and inflammation
1956	Bagby and Janes	Plates with oval holes that allow inter-fragmentary compression during screw tightening	Corrosion and inflammation

Fig.1

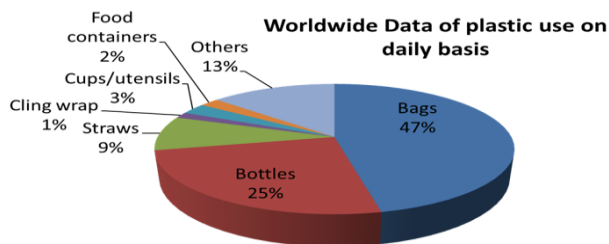
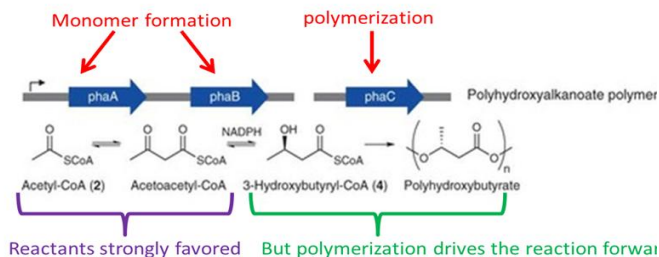


Fig.2



Reaction mechanism of PHAs pathway

Wound dressing

Wound dressing is a technique that may or may not be surgical. This technique involves providing the wound with aseptic or sterilized environment in order to prevent undue contamination of the wound. This technique is basically employed in areas where healing of the wound by itself is difficult and painful. In some cases, wound dressing is employed to apply medication to the wounded area.

Types of dressings

Dressings may be of the following types:

- Sutures
- Staples
- Transparent adhesives
- Clips

Suture: is a largest group of medical apparatus used in wound healing, commonly known as stitches. They may be natural or synthetic. Sutures are used mainly to treat vascular wounds and tissue wounds. Their main purpose is wound closure, it involves a needle attached with a thread, however the size, shape and materials have been drastically evolved with new developments over the years. The sutures are secured with a surgical knot at the end of the wound.

Characteristics:

Biologically inert

Antimicrobial properties

- ease in handling (Pliable)
- have high tensile strength
- non allergic to host
- non carcinogenic
- should be absorbed after serving its function
- must be able to dissolve in body fluids (absorbable sutures)

History: suturing as a technique is not new, this procedure is now known for ages. Physicians have been using suture for thousands of years now. However, with the advancement in the medical and surgical fields, the material used for this procedure has drastically evolved since time immemorial. Ancient records show the use of hair, linen, grass, pig bristles, cotton, silk and animal gut to close wounds, but today we rarely see such suture.

Classification: sutures are classified into two categories:

1. On the basis of origin
 2. On the basis of absorbability
1. On the basis of origin: sutures are further classified as **natural** and **synthetic**.

● Natural suture: are obtained directly from the nature. For example: hair, grass, cotton, pig bristles and dried animal gut (cats).

● Synthetic suture: are those that are artificially synthesised by humans, to serve the purpose of wound dressing. For example: silk, nylon, polyester, stainless steel.

2. On the basis of absorbability: sutures are further classified as absorbable and non-absorbable.

● Absorbable suture: are those, that have the tendency to dissolve themselves in the body fluids, after serving its purpose. The duration in which the suture dissolves itself may vary from 10 days to 8 weeks, depending upon the severity of wound.

For example: catgut suture, Poly-glycolic acid suture, collagen, poly-lactic acid suture etc.

● Non- absorbable suture: are those, that lack the tendency to dissolve themselves in body fluids and thus have to be removed after wound closure.

For example: nylon, polyester, stainless steel, polypropylene etc. (Pillai and Sharma, 2010).

Selection of suture material: Selection of suture material is a complicated process. Today we have a large variety of suture mastering a few properties over the others. No one suture is ideal for all types of surgeries. The tensile strength, its absorption rate, its flexibility and the ease to knot are some of the important considering factors for a surgeon. If suture are not selected judiciously, it may increase the complications of a surgery and also may delay the healing process.

Polyhydroxyalkanoates in suture: For a material to be used as suture, it must not only be biocompatible but also biodegradable. PHA's are polyester, produced by microorganisms. The most common PHA used in suture production is PHB poly(3-hydroxybutyrate) and its related copolymer PHBV poly(3HB-co-3HV).

Both these polymers are biocompatible i.e. are non-toxic to the host and does not produce host immune reactions such as inflammation, necrosis, tumor formation when incorporated in the host body.

Both PHB and PHBV are slow biodegrading polymers and undergo anaerobic biodegradation in the form of sediments, whereas PGA (Poly-glycolic acid) which is still in use as suture is a bulk degrading polymer. PGA being a bulk degrading polymer, has the tendency to accumulate in various parts of the body, since bulk degradation is difficult to remove from the host system. This accumulation of PGA polymer is toxic to the surrounding tissue in the long run. But the slow degrading PHB and PHBV does not get accumulated in the surrounding tissues and is removed from the host system after completing its function.

PHB has a high tensile strength of 40MPa, which makes it suitable for suture preparation as it exhibits the strength necessary for tissue joining, thereby healing the wound.

Presence of foreign materials in wound is known to enhance the infection in wounds. PHB and PHBV do not show any reaction with the foreign material, hence prevent the spread of infection. Another approach to avoid wound infection is the production of antimicrobial suture. This can be done by incorporating silver metal on the surface of PHB or PHBV suture.

Thus, PHB and PHBV have several advantages over the most commercially available sutures. However, the commercialization of PHA as suture is curbed by the high cost of its production.(Dennis *et al.*, 2016)

Drug delivery systems: are artificially engineered medical apparatus used for targeted delivery or control release of the drug. The purpose of the drug delivery system is to control the rate at which drug is released and the site where it is released. Drug delivery systems are of various types, they may be in the form of tablets, nanoparticles, implant patches. Here we are going to focus majorly on the implant patches.

Implant patches: An implant is a device used to deliver drug at a particular site of action or can be used to replace a defect in a biological structure or support a damaged biological structure.

For example: Contraceptive patch: it is a transdermal patch, safe and reliable. When placed on the skin of belly, upper arm, butt or lower back, it releases a hormone that prevents pregnancy.

Implant patches not only have their applications in contraception but also in cosmetics, sensory and neurological disorder, cardiovascular mis-function, orthopaedics.

Properties

- Biocompatible
- Biodegradable
- Non allergic to host
- Non reactive in host system
- Non carcinogenic
- Anti microbial

Types: three major types of implant patches are commercially used:

- i. Stainless steel
- ii. Cobalt- chromium alloy
- iii. Titanium based alloy

Challenges/Complications

i. Stainless steel patches are prone to corrosion, when subjected in the host body. As a result may cause foreign body response, pain, rejection, inflammation (Table 4).

ii. Cobalt-chromium alloy implants: some patients are allergic to metal implants. Introduction of this type of an alloy in such patients can cause an aggressive form of skin cancer in the host, which is now known as the Marjolin's ulcer. Major symptom includes erythema, rash, eczema, swelling and pain.

iii. Titanium based implant: are generally used in orthopaedic devices and oral implants. The accumulation of titanium ions or particulate titanium in the nearby tissues can induce allergic type 1 to 4 reactions.

PHA as implants

PHB based implant patches for gastrointestinal tract on rat model, it was observed that neither an inflammatory

response nor fibrosis was observed with the introduction of this polymer into the host, unlike that observed with the commercially available metal implants.

Similarly, PHBV based implant patches for wound healing in dogs, aged 12 weeks. the dogs were studied until the age of 25 weeks. It was found that it took approximately 7 weeks for complete wound closure and with no observations of foreign body immune response, inflammation or tissue fibrosis. (Chen and Wu, 2005)

PHB can be used as transdermal patches as it is relatively resistant to hydrolytic degradation and it possesses water insolubility, shows great resistance to ultra violet radiations, has high melting point of 175°C, is non toxic to both human and animal host.

Orthopaedic devices: is a medical device, used to correct or treat skeletal deformities in humans and animals.

Fracture fixation: is a term used to refer the stabilization of a broken bone or in simple words when a bone breaks, its pieces get aligned in an unstable manner, which needs to be fixed back to its original location in order to ensure mobility.

There are various devices, commonly referred to as fracture fixation devices which are commercially available and are used to stabilize a broken bone. These devices are of various shapes and sizes and are used accordingly. These include pins, rods, screws, nails, bone plates and many others.

Properties

- Biocompatible
- High modulus of elasticity
- Non corrosive
- Non allergic

- Ductile
- Malleable
- Stiff

History: Internal fixation of fractures is not a new technique, it has been practiced for more than 100 years now. However, the material used for these devices has changed overtime, due to some major complications.

By the mid 20th century, titanium and stainless steel were used to prepare such devices. However these materials still have disadvantages.

Metals have been used in fracture fixation since time immemorial, owing to its high stiffness, strength and low cost, despite the biological responses they produce when introduced into the host system.

Many of the components of stainless steel devices such as chromium (Cr), cobalt (Co), iron (Fe) and nickel (Ni) are known to cause toxicity and effect variety of systems of the host, such as the vascular, immune, excretory, reproductive and nervous system. Also Ni ions are known to cause aggressive skin allergies. Moreover, Ni, Cr and Co are known to interfere the DNA repair mechanism, as a result responsible for altered gene expression. High levels of Cr ions are known to cause hepatocellular necrosis. Ni ions have been shown to increase the mortality due to cardiovascular diseases.

Also Cr ions exposure to mice has shown a decrease sperm count and induced sperm abnormalities, as well as reducing the number of ovarian follicles and ova in mice.

Titanium and titanium based alloys gets degraded into titanium ions or particulate titanium when subjected to friction. The accumulation of these titanium ions is toxic for the surrounding tissues and might cause

toxicity and induce foreign body response, inflammation, tissue necrosis and unwanted pain at the site (Hayes and Richards, 2010).

Complications: Introduction of metals as fixation device into the host may lead to a number of complications such as necrosis, pain, inflammation and may induce a host immune response. Nevertheless, metals are strong and cost effective but are toxic to the host, which may lead to the surgical removal of the entire organ if its toxicity spreads to the neighbouring tissues.

Alternative: PHA as fracture fixation device

PHB poly(3-hydroxybutyrate) and its copolymer PHBV poly(3-hydroxybutyrate-co-3-hydroxyvalerate) can replace the metals in fracture fixation. These are natural polymers, synthesised by various different types of bacteria.

PHB and PHBV are an interesting biopolymer having mechanical strength in compression of 62MPa, which is about the same order of magnitude of several bones in human body and thus can be used in the fracture fixation. Other remarkable properties of this biopolymer is its biocompatibility, shows no host immune response being non-toxic to the host, being water insoluble it can be introduced into the host system without a second thought. Has high modulus of elasticity which makes it strong and replaceable to the metal fixation devices.

Plastics in healthcare industry: Plastic is a dynamic material, development of which has revolutionized almost all the industries. But when we precisely look at the healthcare industry, plastic is almost everywhere; from a small syringe to meter long catheters and large medical packaging. This diversity is observed because of its tendency to be

moulded in any shape and any size. Its light weight, durability, low cost and transparency makes it ideal for the healthcare industry. Some of the most widely used plastics in healthcare are PVC (Poly-vinyl chloride), PE (Polyethylene), PP (Polypropylene), PS (Polystyrene) and PET (Polyethylene terephthalate).

Some plastic material in healthcare industry:

- Syringes
- Gloves
- Coats
- Mask
- Hair and shoe caps
- Disposal bags
- Catheter
- Cannula
- Dropper

Plastics have made the healthcare industry smooth

Advantages

i. Cost effective: plastic production is cost effective. Since the healthcare industry demands large number of plastic based equipments, it becomes difficult to use ceramic, glass or metal equipments because of its high cost and maintenance.

Because of its cost effective nature, single use syringes, gloves and various other equipments are available commercially nowadays, this in turn prevents the spread of various infectious diseases.

ii. Low weight: The low weight of plastic equipment ensures its easy handling.

iii. Can be moulded into any shape: and thus has various applications.

Disadvantages

- Plastic disposal is still a problem. Its non biodegradable nature does not allow its degradation instead results in the release of toxic fumes harmful for both humans and animals.
- Its accumulation in the soil results in release of some toxic substances, thereby polluting the soil as well as the water table.
- Can be carcinogenic

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