ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2013; 4(6): 1107 - 1118

REVIEW ARTICLE

Poly-β-Hydroxybutyrate: Intriguing Biopolymer in Biomedical Applications and Pharma Formulation Trends

Akshay S. Jirage *, Vyankatesh S. Baravkar, Vaishali K. Kate, Santosh A. Payghan, John I. Disouza.

Tatyasaheb Kore College of Pharmacy, Warananagar-416 113, Maharashtra, India

Received 10 Aug 2013; Revised 28 Nov 2013; Accepted 11 Dec 2013

ABSTRACT

The current review focus on optimistic role of Poly-β-hydroxybutyrate (PHB) in pharmaceutical formulation. PHB is a biodegradable thermoplastic which have considerable pharmaceutical importance. PHB biopolymer is effective tool for controlling the drug release profile of formulations. It is an energy-storage polymer both natural and recombinant microorganisms have been used for PHB production. It has been widely used in biomedical applications because of their known biocompatibility and biodegradability. Drug delivery plays an optimistic role in the development of pharmaceutical Formulation for the health care of population. Progress in formulation is achieved by merging of drugs substances into polymeric components to control release of drug from drug polymer complex at a reproducible and predefined rate for an extended time period. This polymeric biomaterial is preferred candidates for developing controlled/sustained release drug delivery vehicles, therapeutic devices such as temporary prostheses. The urge use of PHB in Pharmaceutical and biomedical application because of their bio-acceptance and patient compliance.

Key words: Polyhydroxybutyrate (PHB), Polyhydroxyalkanoates (PHA), Green Plastic, Biopolymer, Biodegradation.

1. INTRODUCTION:

Biodegradable polymers are defined as “materials with ability of functioning for a temporary period and subsequently degrade, under a controlled mechanism, into products easily eliminated in the body metabolic pathways”. The most imperative property of any biodegradable polymer is its constituting monomers and their ratio which in turn decide upon the life of polymer in biological system, physical state, hydrophobicity, flexibility. It is also having properties of degrading in biological fluids with progressive release of dissolved or dispersed drug. The most common synthetic biopolymers produced today are identified by the trade name Biopol®. This biopolymer is the monomers polyhydroxybutyrate (PHB) polyhydroxyalkanoate (PHA) and it is a co-polymer consisting 2 two different monomers joined together, consisting of and polyhydroxyvalerate (PHV). The renewable biopolymers can be produced in nature by microorganism fermentation of sugar or lipids. These polymers include Polyhydroxyalkanoates PHAs) such as poly (hydroxybutyric acid).

Dawes and Senior said Poly-3-hydroxybutyrate (PHB) is linear polyester of D (-)-3-hydroxybutyric acid which was first discovered in bacteria in by Maurice Lemoigne 1926 as a constituent of the bacterium *Bacillus megaterium*. It is accumulated in intracellular granules by a wide variety of Gram-positive and Gram-negative organisms under conditions of a nutrient limitation other than the carbon source. The polymer, which serves as a reserve of carbon and energy [1].

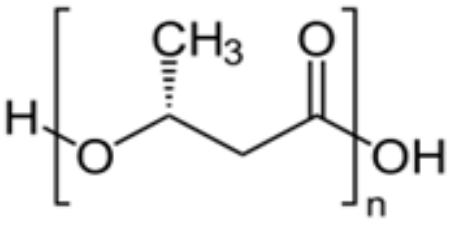

Fig 1: Structure of PHB

***Corresponding Author:** Akshay S. Jirage, **Email:** akshayjirage7@gmail.com

Poly-3-hydroxybutyrate was the first bacterial PHA identified. It has received the greatest attention in terms of pathway characterization and industrial-scale production. It possesses similar thermal and mechanical properties to those of polystyrene and polypropylene. Inevitability to use biopolymer in biomedical area and Pharma formulation because of surgical removal is difficult and bioaccumulation of polymer creates certain toxicological issues. Diffusion controlled drug delivery system is outstanding way to achieve predetermined rate of drug delivery, but drug characteristic and polymer permeability is limited.PHB is one of the good example of energy storage biopolymer. It is synthesized by bacterial source under condition to favorable to their growth. It is gain commercial important now a days because of its matching characteristics with competing polymer such as Polypropylene(PP) and polyethylene (PE) that are produced on large scale. PHB can replace PP and PE because of showing copolymer properties with Polyhydroxyvelarate and matching polymer.PHB has many comparable properties to those PP and PE, In addition where as PP and PE are synthesized from petrochemical source at extreme temperature and pressure.PHB can be produced from many cost effective renewable feedstock by microbial source under less energy consumption and milder condition.

PHB is an efficient energy-storage biopolymer that is screened by number of Gram positive and Gram negative bacteria under favorable conditions to their growth. It is showing similar characteristic feature such as polypropylene (PP) and polyethylene (PE) it is commercially important for the reason that competing portfolio with commercially available polymers. PHB can substitute PP and PE because, of copolymer complex with polyhydroxyvalerate and similar polymers, It has many properties analogous to those of PP and PE. In addition, whereas PP and PE are synthesized from many petrochemical sources at elevated temperature condition and pressure, PHB can be produced from microbes while it is renewable resources with effective ability under less energy-consuming and milder conditions.

Padermshoke said PHB homopolymer is a highly crystalline, stiff, but brittle material. Antipov said when spun into fibres it behaves as a hard-elastic material. Copolymers like PHBV or mcl-PHAs are less stiff and brittle than PHB, while retaining most of the other mechanical properties of PHB. Homopolymer PHB has a helical crystalline structure; this Padermshoke said structure seems to be similar in various copolymers.

PHB is a rare example of hydrophobic polymer that is truly biocompatible and biodegradable with high melting temperature and crystallinity. However, its strength and some other properties such as thermal stability, gas permeability, solvent resistance, and flame retardance are sometimes not enough for end use. Mechanical and thermal properties of PHB have been improved by blending with other biodegradable plastics, such as polylactides. In addition, the structural motifs and crystal structure of melt crystallized PHB produced.

While PHB has a thermoplastic capability and a tensile strength comparable to polypropylene, it's comparatively high crystallinity results in a brittle nature and relatively long degradation time under physiological conditions. However, blending PHB with various additives provides a relatively simple and cost-effective opportunity to manipulate properties of PHB-based biomaterials.

Biosynthetic way for the grounding of PHAs avoids by utilize of initiators, chemical catalysts, and solvents which may reason of tribulations with acceptance of the final formulation if they are not entirely removed in the workup of the polymer complex. PHAs polymer results in macromolecular complex which are characterized by distinctive homogeneity in chirality and regioselectivity of the monomeric units the neat microbial enzymes system contribution of in the formation PHA. The physical-chemical charactristic of the formulated matrices sysytem provide guarantees a high union in the reproducibility. In vitro hydrolytic degradation of PHB profits to the monomer D-3-hydroxybutyricacid which is a ordinary constituent present in blood and, acetone and acetoacetate are common, constitutes three ketone bodies in which one of the formed by the ketogenesis process endogenously. It is, therefore, thought that well tolerance can be shown by PHB *in vivo* condition.

Polyhydroxyalkanoates (PHAs) attract considerable attention as sustainable "green plastics" with a real potential to replace their petrol-based competitors in some applications in the not-too-distant future. To reach this goal PHAs must be able to compete with the established petrol-based plastics in both technical and economic terms. The current PHA production

is based on prized substrates of high nutritional value such as sucrose, starch or vegetable oils. An alternative, carbon-rich industrial waste can be used as a suitable feedstock. This would contribute to making PHAs economically competitive and would avoid the conflict with human nutrition or animal feeding. Consequently, the decision about the location of the PHA-production facilities depends on the preferable in-house availability of such waste streams [2].

New biodegradable polymer blends have been developed to enhance the degradation of the final product. Poly-b-hydroxyalkanoates (PHA) have been attracting much attention in recent years as biocompatible and biodegradable thermoplastics with potential applications.

Poly (3-hydroxybutyrate) (PHB) is one of the well-known biodegradable PHA. PHB is natural thermoplastic polyester and has many mechanical properties comparable to synthetically-produced degradable polyesters used as plasticizer for many pharmaceutical formulations.

2. CLASSIFICATION:

The PHAs producing bacteria can be divided into two groups according to the number of carbon atoms in the monomer units of PHA.

1. Short chain PHAs- These are composed of 3C to 5C monomer units.
2. Medium chain PHAs –These are composed of 6C to 14C monomer units.

These are natural products that are synthesized and catabolised by different organisms and that have found broad biotechnological applications. They can be assimilated by many species and do not cause toxic effect in the host [3-6].

In 1970 Yolles and Sartori discovered the use of a synthetic biopolymer for the systemic delivery of a therapeutic agent. Since that time, a substantial body of literature on drug release from bioerodible polymers has been generated as attention turned to custom- synthesized biodegradable polymers. Three basic approaches have evolved:

1. Erosion of polymer surface with concomitant release of physically entrapped drug.
2. Cleavage of covalent bond between the polymer and drug occurring in bulk or at surfaces followed by diffusional drug loss.
3. Diffusion controlled release of physically entrapped drug, with bio-absorption of the Polymer delayed until after drug depletion [7].

3. METABOLIC PATHWAY INVOLVED IN PHB SYNTHESIS:

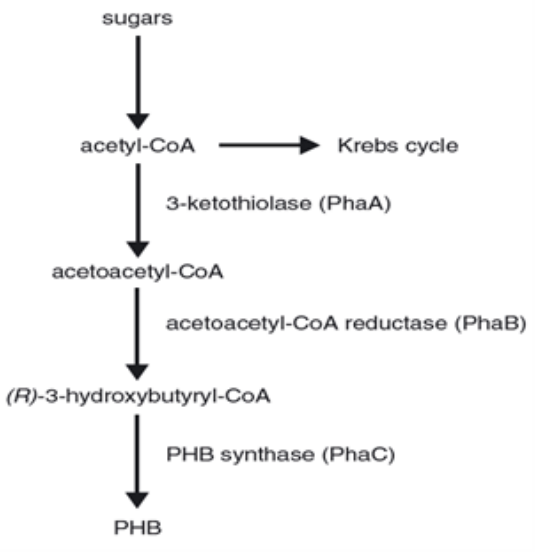

Figure 2: Metabolic Pathway of PHB Synthesis

4. PROPERTIES OF PHB:

- PHB is relatively resistant to hydrolytic degradation and it posses water insolubility. A currently available biodegradable plastic differentiates from PHB because of water solubility or moisture sensitivity properties.
- PHB is good oxygen permeable polymer candidate.
- PHB have a poor resistance to acids and bases but good ultra-violet resistance.
- PHB shows good solubility characteristic in chloroform and different chlorinated hydrocarbons.
- Biocompatible property is potential evidence for its use in biomedical applications and Pharma formulation trends.
- Melting point 175°C and glass transition temperature 2°C.
  Ttensile strength at 40 MPa shows by PHB, close to that of polypropylene.
- PHB showing anaerobic biodegradation process because of it is sinks in water; while polypropylene floats.
- Nontoxic. Less sticky.

5. WHY DO WE PREFER PHB AS BIODEGRADABLE POLYMER?

Few are the general properties of biodegradable polymers:

- The key advantages take in consideration because of its ability to tailor mechanical properties.

- PHB have their backbones which have advantages in terms of good drug delivery kinetics suitable for various applications.
- PHB have attractive fabrication characteristic makes it liable for convert in various shapes with morphologic features in pore formation.
- PHB have capability to hold on entrapped or encapsulated compound.
- PHB polymer can be fabricated with chemical functional groups that can induce tissue in-growth.

6. NEED FOR PHB AS BIODEGRADABLE POLYMER:

- It was recognized that the surgical removal of a drug depleted delivery system was difficult yet leaving non-biodegradable foreign materials in the body for an indefinite time period caused toxicity problem.
- While diffusion controlled release is an excellent means of achieving controlled drug delivery, it is limited by the polymer permeability and the characteristics of a drug increase, its diffusion coefficient decrease.
- There is no need for a second surgery for removal of Polymers.
- Avoid stress shielding.
- Offer tremendous potential as the basis for controlled drug delivery.

7. ADVANTAGE OF PHB AS BIODEGRADABLE POLYMER:

- It provides a drug at a constant controlled rate owes a prescribed period of time.
- The polymer carrier would degrade into nontoxic, absorbable Subunits which would be subsequently metabolized.
- The system would be biocompatible would not exhibit dose dumping at any time and polymer would retain its characteristics until after depletion of the drug.
- Degradable system eliminates the necessity for surgical removal of implanted device following depletion of a drug.
- PHB biologically broken down into acceptable molecules which comprise capability to that are metabolized in the system and removed from the body via usual metabolic pathways.

8. FACTOR AFFECTING ON BIODEGRADATION OF POLYMERS:

- Chemical structure.
- Chemical composition.
- Repeat units in multimers by distribution phenomenon.
- Presents of ionic groups.
- Presence of chain defects or unexpected units.
- Configuration structure.
- Molecular-weight distribution.
- Morphological parameter like microstructures, amorphous/semicrystalline, residual stresses.
- Presence of low-molecular-weight compounds.
- Processing conditions.
- Annealing.
- Sterilization process.
- Storage history.
- Shape.
- Site of implantation.
- Physicochemical factors (PH ionic strength, ion exchange).
- Mechanism of hydrolysis (water versus enzymes).
- Physical factors (variations of diffusion coefficients, size and shape changes, mechanical stresses, solvent-induced cracking and stress, etc.).
- Absorbed adsorbed and compounds (ions, lipids, water, etc.).

9. MICROBIAL SOURCE FOR PHB SYNTHESIS [8]:

PHAs are produced by variety of different microbial cultures. *Cupriavidus necator* (formerly known as *Alcaligenes eutrophus* or *Ralstonia eutropha*) is the bacterial source one that has been most broadly used in large scale production. Imperial Chemical Industries (ICI plc) is the innovator they firstly used bacterial strain for the production of PHBV copolymer under the trade name BIOPOL™.

Now days, bacterial fermentation process seems to be the most cost-effective process for *Cupriavidus necator* ,even if production switches to agricultural crops or other bacteria, these processes are likely to use *Cupriavidus necator* genes. A number of bacterial strains that were recently studied in which few important other strains include: *Alcaligenes* spp

Bacillus spp., *Pseudomonas* spp., *Burkholderia sacchari Aeromonas hydrophila*, Escherichia *coli*, *Rhodopseudomonas palustris* and *Halomonas boliviensis*. (**Table 1**) shows the list of bacterial source used to produce PHAs, including their corresponding initial carbon sources and produced (co)polymers.

Table 1: Microbial Species for PHB Production

Alcaligenes latus
Bacillus spp.
Burkholderia sacchari sp. nov.
Burkholderia cepacia
Caulobacter crescentus
Escherichia coli mutants
Halomonas boliviensis
Legionella pneumophila
Methylocystis sp.
Microlunatus phosphovorus
Pseudomonas aeruginosa
Pseudomonas oleovorans
Pseudomonas putida
Pseudomonas stutzeri
Rhizobium meliloti, R. viciae,
Rhodopseudomonas palustris
Spirulina platensis (cyanobacterium)
Staphylococcus epidermidis
Cupriavidus necator
Cupriavidus necator H16 etc.

PRIMARY CONFIRMATION OF PHB GRANULES:

Primary confirmation of PHB granules production in bacteria is observed by Sudan black-B staining method.

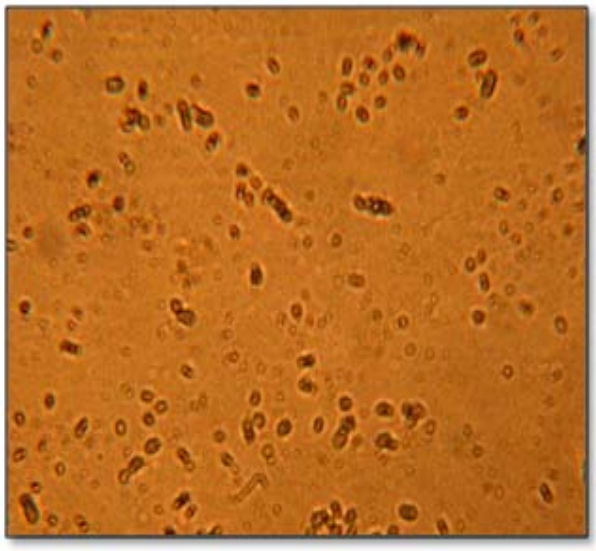

Figure 3: Sudan black-B stained PHB granule

(Image courtesy By: Alok Kumar and Prateek Singh SRM University)

Juvan said Sudan Black B staining 0.02 per cent solution of Sudan Black B in 96 per cent ethanol and simply flood the plate with this solution keeps it for half hour and wash with water PHB granules showing black colour this thing confirms the primarily PHB presence.

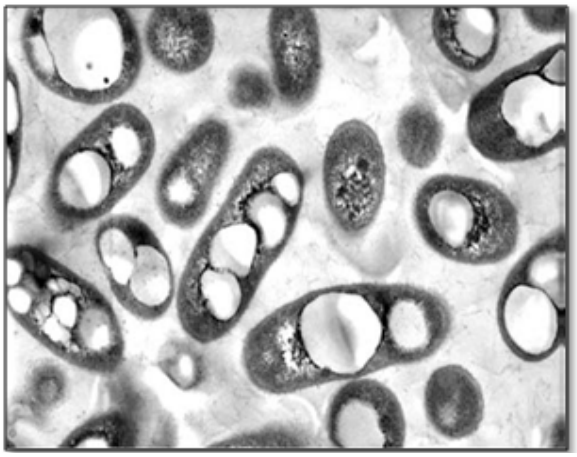

Figure 4: STEM picture of *Cupriavidus necator* cells harboring PHB biopolymers

(Image courtesy By: Martin Koller, Graz University of Technology, Graz, Austria)

10. DIFFERENT SYNTHESIS PATHWAYS INVOLVED IN PHB:

PHA's are synthesized either by chemical means or by biological approaches.

1. Pathway-I Enzyme involved are:
   - I. β-keto thiolase
   - II. PHA synthetase
   - III. NADPH dependant acetoacetyl CoA reductase
2. Associated pathway Enzyme involved are:
   - I. PHA depolymerase
   - II. Dimer hydrolase
   - III. 3-hydroxybutyrate dehydrogenase
   - IV. Acetoacetyl CoA oxidase
   - V. Acyl-CoA oxidase
   - VI. Enoyl-CoA hydratase
3. Pathway- II Enzyme involved are:
   - I. 3-ketoacyl CoA reductase
   - II. Acyl-CoA oxidase
   - III. Enoyl CoA hydratase
4. Pathway-III Enzyme involved are:
   - I. 3-hydroxyacyl CoA transferaase
5. Pathway-IV Enzyme involved are:
   - I. NADH-dependant acetoacyl CoA reductaase
   - II. Succinic semialdehyde dehydrogenase
   - III. 4-Hydroxybutyrate-CoA:CoA transferase
6. Pathway-V Enzyme involved are:
   - I. 4-Hydroxybutyrate dehydrogenase
   - II. 4-Hydroxybutyrate-CoA transferase
7. Pathway-VI Enzyme involved are:
   - I. Lactonase
   - II. Hydroxyacyl-CoA Synthase
8. Pathway-VII Enzyme involved are:

I. Alcohol dehydrogenase

9. Pathway-VIII Enzyme involved are:
   I. Cyclohexanol dehydrogenase 6-hydroxyhexanoate dehydrogenase
   II. Hydroxyacyl CoA synthetase

12. PHB POLYMERASE:

PHB polymerase is also one of the enzyme in the biosynthetic pathway for PHB production.PHB Polymerase is the member of the PHAs polymerase family. All of the polymerases have a molecular mass of around 63,000 Da, except for some of the polymerase which is composed of subunits with molecular masses of 40 and 45 kDa. PHAs polymerase is found in both soluble and granule-bound a number of PHAs-producing microorganisms represent a spectrum of intracellular conditions to which these enzymes would have to be adapted [9].

Polyhydroxybutyrate (PHB) offers many advantages over traditional petrochemically derived plastics. In addition to its complete biodegradability, PHB is formed from renewable resources. It possesses better physical properties than polypropylene for food packaging applications and is completely nontoxic. The poor low-impact strength of PHB is solved by incorporation of hydroxyvalerate monomers into the polymer to produce polyhydroxybutyrate-co-valerate (PHBV), which is commercially marketed under the trade name BIOPOL™. Like PHB, PHBV degradation entirely occurs into carbon dioxide and water under aerobic circumstances. Microbial synthesis of PHB is the best method for industrial production because it ensures the proper stereochemistry for biodegradation. Microorganisms synthesize and store PHB under nutrient-limited conditions and degrade and metabolize it when the limitation is removed. Current production employs *Alcaligenes eutrophus* because it grows efficiently on glucose as a carbon source, accumulates PHB up to 80% of its dry weight, and is able to synthesize PHBV when propionic acid is added to the feedstock. PHBV is currently 16 times the price of polypropylene. However, the development of transgenic PHA-producing organisms is expected to greatly reduce its cost. Benefits of using transgenic systems include lack of a depolymerase system, ability to use faster-growing organisms, production of highly purified polymers, and ability to utilize inexpensive carbon sources. Because transgenic plants may someday result in the evolution of plastic crops that could lower the price of PHA to a competitive level, future research will surely focus on such recombinant DNA techniques [10].

13. DRUG RELEASE MECHANISM FROM BIODEGRADABLE POLYMER SYSTEM:

Biodegradation of polymer occur within the body by means of natural biological process. The elimination of active agents is needed after drug delivery system interval. Fabrication of most of biopolymers such as they degrades as a result of hydrolysis of chain structure polymer into progressively smaller and biologically acceptable compounds. In some biodegradable polymer notably most the polyorthoesters and polyanhydride degradation process occur at surface area of the drug delivery system. The need of investigation of biodegradable polymer mainly because of application either from synthetic or natural origin.

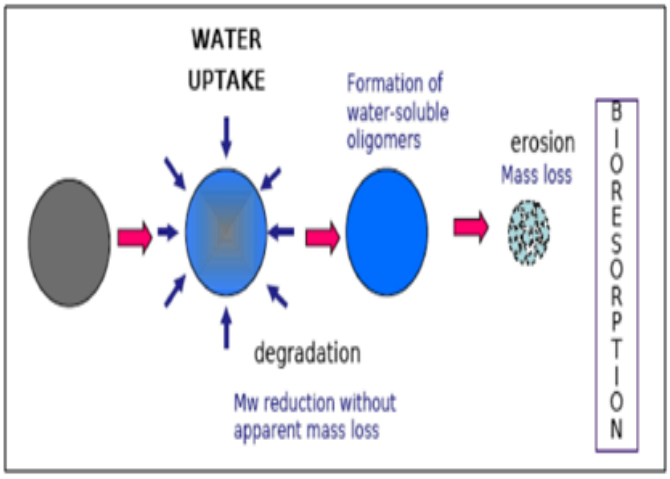

Figure 5: Drug release mechanism from Biodegradable polymer system

14. Table 2: Solubility of PHB in different Solvents:

Highly soluble in	Poorly soluble in	Practically insoluble in
Chloroform	Toluene	Water
Dichloromethane	Benzene	Methanol
Acetic anhydride		Ethanol
Sodium Hydroxide		Hexane
Acetic acid		Benzene

15. BIOCOMPATIBILITY OF PHB :

15.1 BIOCOMPATIBILITY OF PHB *IN VITRO*:

Biocompatability of PHA in vitro has been demonstrated at different cell cultures: fibroblasts, mesenchymal stem cells, osteoblasts, bone marrow cells, articular cartilage chondrocytes, endothelial cells, smooth muscle cells etc.

Bonartsev said Biocompatibility of PHB at cell cultures isolated from monkey kidney AGMK and FRLK4 grown on PHB films as on scaffolds for 3-60 days. PHB didn't influence on growth and

vitality of cells for whole period of cell cultures incubation. The cells were not exposed to any polymer-depending factors: delivering toxic substances (products of polymer destruction), incompatible polymer surface etc. We have examined also the cytotoxicity of extract from PHB films at the same cell cultures. The addition of the extract to cell cultures grown on laboratory plastic Petri dishes didn't influence on growth, development and migration of the cells. The index of cytotoxicity was evaluated as 0.84 that indicates that PHB is not toxic. Thus, PHB is biologically inert and highly biocompatible for isolated cell cultures *in vitro*.

15.2 BIOCOMPATIBILITY OF PHB

***IN VIVO*:**

Bonartsev said Biocompatibility of PHB has been demonstrated in vivo under subcutaneous implantation of PHB films. Tissue reaction to films from PHB of different Mw (300, 450, 1000, 1500 kDa) implanted subcutaneously was relatively low and didn't change from tissue reaction to control glass plate. The low tissue reaction to implanted PHB films indicates the high biocompatibility of PHB in vivo that was observed by many investigators. The possible reason of high biocompatibility of PHB is presence of natural PHB oligomers and 3-hydroxybutyrate, the intermediate product of PHB degradation, in animal tissues at normal conditions in comparison with chemically synthesized biodegradable polymers, for example, polylactides and polyglycolides. Toxicological certificate of Institute of Medical Technique (Ministry of Health, Russia) that approves of PHB for application in medicine as nontoxic and biocompatible material suitable for implantation in human tissues.

16. CURRENT STATUS AND FUTURE TRENDS:

The use of bio-based material in the chemical sector is not a novel concept. They have been industrially feasible on a large scale for more than a decade. Additive-based chemistry developed for improving the performance and processing of fossil fuel-based polymers, and this knowledge can be used to develop new additive chemistry to improve the performance and properties of bio-based polymers. For bio based polymers like PLA and PHA, additives are being developed to improve their performance, by blending with other polymers or making new copolymers. However, the use of nanoparticles as additives to enhance polymer performance has long been established for petroleum-based polymers. Various nano-reinforcements currently being developed include carbon nanotubes, graphene, nanoclays, 2-D layered materials, and cellulose nanowhiskers. Combining these nanofillers with bio-based polymers could enhance a large number of physical properties, including barrier, flame resistance, thermal stability, solvent uptake, and rate of biodegradability, relative to unmodified polymer resin. These improvements are generally attained at low filler content, and this nano-reinforcement is a very attractive route to generate new functional biomaterials for various applications.

Delivery of drugs for clinical treatment is a challenging problem. A programmed release of drug at specified levels is optimal for various types of clinical treatments including cancer therapy. Encapsulation of drugs in biodegradable polymeric nanospheres is a recent technology that offers significant advantages over conventional therapies. An important issue is the binding efficiency of a specific drug to different types of polymers.

Recent advances in transplant surgery and introduction of new materials in medicine have made biological safety of medical items, such as primarily implants, a critical issue. The materials for fabricating temporary implants (sutures, artificial pericardia, stents, etc.) must be not only biocompatible, but also prone to biodegradation, forming products that are non-toxic to the organism. Finding materials possessing these balanced properties is a great challenge. Implants made from biodegradable materials tissues, and to be controllably degraded once they have been replaced by native biological structures. It is generally recognized that biomedical-grade materials, intended to contact living organisms, must possess a complex set of necessary biological and physical mechanical properties. They must be biocompatible at the level of cultured cells and tissues of the microorganism and non-toxic both before and after degradation. These materials must also fulfill a supportive function for cells, favor their proliferation and differentiation, allow for availability of growth substrates, and allow for release of metabolites. The material must possess proper mechanical strength and flexibility; have tissue growth favorable surface characteristics, be tolerant of conventional sterilization methods and the effects of aggressive biological media, while also being

easy to process using conventional production methods. Comprehensive preclinical investigations of Polyhydroxyalkanoates, including in vitro assay systems and short- and long-term exposure experiments on laboratory animals, have shown that PHAs of different compositions, in this case produced by and purified from *R. eutropha* strains, can be regarded as medical grade materials. Polymers and polymeric items, such as film-based tissue engineering scaffolds and suture fibers, were evaluated in conventional and sanitary chemical, toxicological, and biomedical tests.

Lafferty and Lee said that P(3HB) and D(-)-3-hydroxybutyric acid, is degradation product of a ordinary intermediate metabolic component in all higher organisms. Therefore, it is reasonable that it is shows biocompatibility to P(3HB) and animal tissues so it can be can be implanted in animal tissues without any noxious effect. Some potential applications of bacterial PHAs in the biomedical and pharmaceutical applications consist of: To attain long term dosage of drugs by biodegradable carrier inside the body, sutures, surgical pins, and wound dressing, swabs, plates, and bone replacements blood vessel replacements, healing and stimulation of bone growth by piezoelectric properties. The benefit of using biodegradable polymer during implantation because of its biodegradability i.e., no need for surgical removal. Wang and Bakken said that biodegradable carriers for long period dosage of drugs PHAs mostly be used, hormones and medicines. Brandl said that used as osteosynthetic materials in the stimulation of bone growth owing to their piezoelectric properties in bone plates, surgical sutures and blood vessel replacements.PHA as a source for the synthesis of chiral compounds (enantiomerically pure chemicals) and raw materials for the production of paints. PHA could be depolymerized to rich source of optically active pure bifunctional acids. PHB, for instance, is readily hydrolyzed to R-3- hydroxybutyric acid and used in the synthesis of Merck's antigaucoma drug 'truspot' in tandem with r-1,3-butanediol. It is also used in the synthesis of beta lactams.

Biodegradable polymers are important materials for clinical applications in medicine. For example, polylactic acid is widely used as a dissolvable suture or stent, and also for dialysis media and drug delivery devices. Absorption of water into the polymer system leads to beginning of physical biodegradation process. This study focuses on water uptake for a library of tyrosine-derived polymers (polyarylates). Experiments are performed for measuring water uptake at discrete time points up to twenty eight days using a radioactive labeling technique. Bioinformatics methods are used to predict water uptake for the entire library of polyarylates based upon experimental measurements for a subset of the library.

There has been a considerable interest in development of biodegradable polymers such as polyhydroxybutyrate (PHB) from bacterial origin which could help in solving probable problems due to use of synthetic polymers. Many synthetic polymers are being used now-a-days in drug delivery systems. But synthetic polymers have certain disadvantages such as their non-biodegradability and so probability of bioaccumulation. Such accumulations for long time in body are not good. This explains a need of easily biodegradable polymer. Bacteria can synthesize a wide range of biopolymers which are biodegradable, biocompatible and have material properties suitable for medical applications. Bacterial polymers such as PHB, if modified to make functionally more effective can be better for use in pharmaceutical field. These studies started with screening of better producer of PHB from soil. This paper represents a work on screening of bacterial isolates capable of producing PHB, and production of PHB using laboratory scale fermentation procedures. Using nutrient agar Shaikh K could screen four bacteria from soil, capable of producing PHB, using Sudan black-B staining. He also used a pure bacterial culture of *Alcaligenes latus* obtained from MTCC Chandigarh as a producer of PHB. Out of these five bacterial isolates, *Alcaligenes latus* found producing PHB in relatively more amounts yielding about 25%. He used *Alcaligenes latus* for production of PHB in large quantity [16] Patwardhan and Srivastava said that PHB used in surgical materials or as a slow-release carrier for long-term drug delivery.

17. PHARMACEUTICAL AND BIO-MEDICAL APPLICATIONS:

An extensive range of biopolymers have been used for biomedical application including surgical treatments, preventive medicine, and clinical inspections of diseases[11.] PHAs also have numerous medical applications. The main advantage in the medical field is that a biodegradable plastic can be inserted into the human body and does not need to be removed again. Zinn said that PHA has posses ultimate

biocompatibility characteristic as it is a product of cell metabolism and also 3-hydroxy butyric acid (the product of degradation) this normally constitute between 0·3 and 1·3 mmol l−1 in blood at concentrations. In composites or as pure form with other materials, PHAs are used as repair patches, sutures, nerve guides, orthopedic pins, bone marrow scaffolds ,stents, and adhesion barriers,. An interesting aspect of PHA scaffolds is the fact that the tissue-engineered cells can be implanted with the supporting scaffolds. Research shows that PHA materials can be useful in bone healing processes. Chen and Wu said that PHA together with hydroxyl Apatite (HA) can find an application as a bioactive and biodegradable composite for applications in hard tissue replacement and regeneration. Polymer implants for targeted drug delivery, an emerging medical application, can be made out of PHAs. However, because of the high level of specifications for plastics used in the human body, Vert said that not every PHA can be used in medical applications. Sevastianov said that PHA used in contact with blood has to be free of bacterial endotoxins and consequently there are high requirements for the extraction and purification methods for medical PHAs.

Zinn said that it has immense potential for medical applications, such as orthopaedy (bone graft substitute and scaffolds for cartilage engineering), dental (barrier material for guided tissue regeneration), wound management (sutures, skin substitute, surgical swabs and surgical staples), and urological stents.

17.1. Wound management:

- Sutures
- Staples
- Clips
- Adhesives
- Surgical meshes

17.2. Orthopedic devices:

- Pins
- Rods
- Screws
- Tacks
- Ligaments

17.3. Dental applications and Maxillofacial:

- Guided tissue regeneration Membrane
- Guided bone regeneration
- Void filler following tooth extraction

17.4. Cardiovascular applications:

- Cardiovascular Stents
- Vascular Grafts
- Pericardial patch
- Heart valve

17.5. Intestinal applications:

- Anastomosis rings

17.6. Drug delivery system:

- Implants and Tablets
- Microparticulate carriers
- Prodrugs

17.7. Tissue engineering:
17.8. Nerve Repair:
17.9. Artery agumentation:
17.10. Genotoxicity

18 .TISSUE ENGINEERING:

Cairns, Rastrelli, Kirsner, Phillips, Teumer told that Two-dimensional matrices, in the form of thin films, have special applications in tissue engineering. The earliest and most successful application of 2D matrices in tissue engineering is the regeneration of skin. As a result of the work done in this area for the past two decades, skin regeneration has now become a reality. However, the products today still have their shortcomings, including the lack of the mechanical properties in the skin graft and the risks of immunological rejection. Studies are still being conducted with the objective of improving the present techniques in skin regeneration [14].

19. WOUND DRESSING:

Polymer films have been investigated in the development of a synthetic burn covering since the mid 1970s. To be employed as wound dressing, it should be durable, stress resistant, flexible, pliable and elastic. It should be easy to apply and remove without incurring any trauma during dressing changes. As such, the mechanical properties of the films are critical and important to be characterized. Films should possess reasonable tensile properties, which could bear the stresses exerted by different parts of the body having varying contours. Furthermore, the dressing is preferably permeable to water vapour to the extent that moist exudates under the dressing is maintained without pooling, but excess fluid absorption and evaporation leading to desiccation of the wound bed are prevented. It has reported that the control of moisture loss is of utmost importance to immediate survival and ultimate recovery of a burn patient. Control is the key concept since an impermeable membrane may foster and perpetuate fluid-up between the

biomaterial and the wound surface, producing a hot, moist environment in which sepsis thrives. A covering that is too permeable will not be an effective barrier to caloric loss. Hence a wound dressing with suitable fluid control is required. Widra also published that the dressing must be compatible with body tissues, be nontoxic, non-antigenic and non-allergic.

20. CONTROLLED DRUG DELIVERY:

There has been growing interest in subject of drug delivery and design and evaluation of controlled release system. Controlled release dosage forms are the convenient means obtain a reduction of daily administration of drug with fast absorption and elimination. Many controlled release system have been developed for maintain a therapeutically effective concentration of drug in systemic circulation for longer period of time as to reduce side effects.

Polymer-based controlled release systems are normally classified as either reservoir (membrane) devices or matrix (monolithic) devices. In this system by means of polymeric membrane former type release is controlled that surrounds a drug containing reservoir. Various types of polymeric membrane may be used in the construction of reservoir devices. In general, these types may be sub-divided into hydrophobic, non-porous membranes, microporous membranes and water-swollen, hydrophilic membranes (hydrogels) [15].

Interest in the use of polymers as rate-controlling films for transdermal drug therapy is indicated by patent reports. Drug release rate is controlled by diffusion across this surrounding membrane so that neither dissolution nor degradation of the polymer should occur during the active lifetime of the device. The number of important applications carryout by permeability, together with other properties of polymers, forms a basis of a, one of such being the tablet coating.

The Potential use of poly 3HB found in the polymer implants, Microparticulate carrier,press coated tablet for oral administration [16].

21. TRANSDERMAL PATCHES:

Transdermal drug delivery is a device that maintain blood concentration of drug within the therapeutic window ensuring that drug levels concentration nor exceed the minimum toxic dose. Transdermal drug delivery offers many advantages such as reduced side effects, less frequent administration to produce the desired constant plasma concentration associated with improved patient compliance, elimination of the first pass effect, sustained drug delivery and interruption of treatment when necessary [17,18].

22. MICROSPHERES:

Bidone said the incorporation of drugs into polymeric microspheres can be employed in the pharmaceutical field for various purposes including the controlled-release of the drug in order to maintain therapeutic drug levels over a specified time period. Bidone said that PHB and PHBV have been used to prepare micro- and nanoparticles containing ibuprofen [19].

23. COMPOSITE:

Particulate hydroxyapatite (HA) was incorporated into polyhydroxybutyrate (PHB) to form a bioactive and biodegradable composite for applications in hard tissue replacement and regeneration [20, 21].

Polyhydroxybutyrate (PHB) is a biomaterial with potential for applications in biomedical and tissue engineering; however, its brittle nature and high crystallinity limit its potential. Blending PHB with a variety of PEGs produced natural-synthetic composite films composed of FDA-approved polymers with significant reductions in crystallinity [22].

24. CARDIAC STENT:

The latest advance in the field of nanotechnology most pronouncedly appeared in construction of cardiovascular stents. First and foremost, this concerns the main concept in design of the stents that provide a prolonged and local drug delivery. In addition, the obligatory requirement to cardiovascular stents is effective biocompatibility (hemocompatibility). The combination of controlled drug delivery and biocompatibility may be attained by nano structuring the surfaces of cardiac implants, e.g., constructing meso and nanoporous layers responsible for controllable release, protein adsorption, and adhesion of blood cells (platelets, erythrocytes, leukocytes, etc.) [23].

25. IMPLANTS IN UROLOGY:

Biodegradable polymers represent a separate group of polymer implants in urology. By analogy with bioresorbable suture materials and nanoparticles, the following groups of natural polymers have been used for their production: poly (α_oxyacids) (polylactides and their copolymers) and poly (β oxyalkanoates) (PHAs and the copolymers with oxyvalerate, oxyhexanoate, etc.). An example is the multifunctional implanted system Zoladex, which

was designed over 20 years ago and is currently widely used in clinical practice for the long term therapy of endometriosis, breast tumors, and prostate tumors [24].

26. NANOPARTICLES AS INTRACELLULAR SUSTAINED DRUG-RELEASE VECTORS:

Poly-R-3-hydroxybutyrate (PHB) was the first found PHA homo-polymer that has been investigated most intensively for various applications due to its ease of production.

Polyhydroxybutyrate (PHB), co-polyesters of 3-hydroxybutyrate and 3-hydroxyhexanoate (PHBHHx), and polylactic acid (PLA) were used to prepare nanoparticles with average sizes of 160, 250 and 150 nm, respectively [25].

Poly(hydroxybutyrate) (PHB)/layered silicate nanocomposites were prepared via melt extrusion.[26] nanoparticles such as nanoclays to form nanocomposites has provided the means to improve materials performance including biodegradation. One advantage of clay nanocomposites is their improved barrier properties while retaining the flexibility and optical clarity of the pure polymer [27-31].

27. FUTURE PERSPECTIVES:

- Immunoisolation.
- Hydrogels of Stimuli-responsive polymers.
- Proteins or DNA encoding a protein use as biodegradable polymer release systems.
- Improve the processing of biodegradable polymers (nanocomposites).

28. CONCLUSION

The biodegradable polymer such as PHB have established much more attention in the devolvement of biomedical and Pharma formulation trends since from last decades due their potential applicable contribution in the field. This enacted as an eco-friendly protection providing polymer; and that improve maintenance of physical health. To attain progress in the properties of biodegradable polymers, a lot of conformational methods have been developed, such as random and grafting or block copolymerization.

These methods can able to improve both the mechanical properties and biodegradation rate of the finished products. Potential use biopolymer such PHB have proven for the development of new, efficient and drug advanced delivery system and prompt biomedical practices. They are capable of delivering a wide range of bioactive materials. Today the stress is on patient compliance and to achieve this objective there is spurt in development of NDDS.

- Uses of biodegradable polymers are being unraveled to be a long way to go.
- Currently promising biodegradable applications are under investigation for Nanocomposites.
- Zero-order Release profile cannot be achieved due to combination of diffusion and erosion processes.
- Using biodegradable delivery systems such as microspheres or implants for proteins can be possible with help of Solvent free Methods to avoid Stability problems.

REFERENCES

1. Dawes E. Polyhydroxybutyrate an Intriguing Biopolymer, Bioscience report, 1988; 8 (6): 537-538.
2. Koller M, Salerno A, Muhr A, Reiterer A, Braunegg G. Polyhydroxyalkanoates: Biodegradable Polymers and Plastics from Renewable Resources, 2013; 47 (1):23-30.
3. Steinbuchel A, Fuchstenbusch B. Bacterial and other biological systems for polyesters production. Trends Biotech, 1998; 16, 419-427.
4. Angelova N, Hunkeler D. Rationalizing the design of polymeric biomaterials.Trends Biotech. 1999; 17,409-421.
5. Zinn M, Witholt B, Egii T. Occurrence synthesis and medical application of bacterial polyhydroxyalkanoate. Adv Drug Rev, 2001; 53, 5-21.
6. Williams S.F, Martin D. Application of PHA's in medicine and Pharmacy Applications and commercial Products. 2002; Germany: Wiley VCH, **7**; 4: pp 91-128,**.**
7. Joshi J R, Patel R.P. Role of biodegradable polymers in drug delivery. International J Current Pharma Research, 2012; 4 (4): 74-81.
8. Verlinden R, Hill D, Kenward M, Williams C, Radecka I. Bacterial synthesis of biodegradable Polyhydroxyalkanoates. Journal of Applied Microbiology, 2007; 102 (6), 1437–1449.
9. Libergesell M, Sonomoto M, Madkour F, Steinbuchel M.Purification and Characterization of poly(hydroxyalkanoic acid) synthase from chromatin vinosum and localization of the enzyme at the

surface of poly(hydroxyalkanoic acid) granules. Europe Journal of Biochemistry, 1994; 226, 71-80.

10. Hankermeyer C, Tjeerdema R. Polyhydroxybutyrate: plastic made and degraded by microorganisms. Rev Environ Contam Toxicol, 1999, 159, 1-24.
11. Shalaby M, Ikada Y, Lander R, Williams J. Polymers of Biological and Biomedical Significance. ACS Symp. 1994 Ser. 540.
12. Chu C, Fraunhofer L A, Greisler H. P. Wound Close Biomaterials and Devices. 1996; CRC Press, New York.
13. Atala A, Mooney D, Vacanti J, Langer R. Synthetic Biodegradable Polymer Scaffolds. 1997. Birkhauser, Boston.
14. Ikada Y. Tissue Engineering Research Trends at Kyoto University, In Tissue Engineering for Therapeutic Use, American. Chem. Socaity. 1998., Washington, DC, 1–14.
15. Horoshi S, Yasuhiko M, Toshio O, Masaharu M; Hisakazu S. Dissolution mechanism of diclofenac sodium from wax matrix granules Journal of pharmaceutical Science, 1997; 86,929-932.
16. William S, Martin D Application of PHA in Medicine and Pharmacy. Applications and commercial Products. Germany: 2002; Wiley VCH, 4: 91-128.
17. Jing A, Weimin S. The adverse drug reaction of indapamide. Pract. J.Med. Pharm, 2003. 11, 843-844.
18. Smith R, Stewart J. Procurement and characterization of standard reference material1981; 4,256-258.
19. Bazzo C, Macedo A, Crenca J, Silva V, Pereira M, Zétola M, Pezzini B. Microspheres prepared with biodegradable PHBV and PLA polymers as prolonged-release system for ibuprofen: *in vitro* drug release and *in vivo* evaluation. Brazilian Journal of Pharmaceutical Sciences 2012; 48(4): 773-780.
20. Wang M, Ni J. *In vitro* evaluation of hydroxyapatite reinforced polyhydroxybutyrate composite. Materials Science and Engineering. 2002; 20,101–109
21. Loge F, Erik R, Coats A, Michael P, Wolcott C, Karl Englund K; McDonald A. Production of natural fiber reinforced thermoplastic composites through the use of polyhydroxybutyrate-rich biomass. Bioresource Technology. 2008. 99, 2680–2686.
22. Rodman T, Chan H, Russell R, Holden P, Foster J. Application of Polyethylene Glycol to Promote Cellular Biocompatibility of Polyhydroxybutyrate Films. Hindawi Publishing Corporation, Int J Polymer Sci; 2011. 1-9.
23. Iordanskii A, Rogovina S, Berlin A. Current State and Developmental Prospects for Nanopatterned Implants Containing Drugs. Rev J chem. 2013; 3, 2,117–132.
24. Hutchinson F; Furr B. Journal of Control. Release. 1990; 13, 279,
25. Xiong Y, Yao Y, Zhan X, Chen G. Application of Polyhydroxyalkanoates Nanoparticles as Intracellular Sustained Drug-Release Vectors. Journal of Biomaterials Sci. 2010; 21, 127–140.
26. Maiti P, Carl A, Battand E, New Biodegradable Polyhydroxybutyrate/Layered Silicate Nanocomposites, Biomacromolecules, 2007; 8, 3393-3400.
27. Lim S, Hyun Y, Choi H; Jhon, M. Chem. Mater. 2002; 14, 1839.
28. Maiti P, Yamada K, Okamoto M, Ueda K, Okamoto K; Chem. Mater. 2002.14, 4654.
29. Ray S, Maiti P, Okamoto M, Yamada K, Ueda K. Macromolecules. 2002; 35, 3104,
30. Ray S S, Yamada K, Okamoto M, Ogami A, Ueda K. Chem. Mater. 2003.; 15, 1456.
31. Lee S. R, Park H. M, Lim H, Kang T, Li X, Cho W. J, Ha C. S, Polymer. 2002; 43, 2495.