Biodegradable microbial poly-alkanoates as heart stents: production, uses and its current status

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ABSTRACT

Innovative biopolymer materials have been a zone of enthusiasm for some researchers for use in different areas. Biodegradable polymers are accepted to be condition cordial and monetarily modest. These are ordered into Natural polymers and Synthetic polymers. Normal polymers can be acquired from animals, marine source, farming or microbial source. Polymers got from the microbial sources incorporate polyhydroxyalkanoates (PHAs) and polylactic corrosive (PLA). Utilization of PHAs and PLAs in pharmaceutical and medicinal instruments has increase tremendous considerations. Drug Eluting Stent (DES) has clinical significance as another option to Coronary Artery Bypass Grafting because of the simple methodology and similar security and viability. The presence of a permanent device might affect negatively. So, a biodegradable stent is fitting as an answer. This review plans to give a updated knowledge into the present status of absorbable metal outlines, substantial scale generation of microbial biopolymers and their utilization as heart stents.

Keywords: Biodegradable polymers, PHB, PLA, DES; heart stents, angioplasty, restenosis.

INTRODUCTION

Fitting of new materials inside a point of view of eco-plan or economic advancement is a theory which is connected to an ever-increasing number of materials; a motivation behind why biodegradable polymers are considered as earth safe options. Moreover, renewable resources-based items are aftereffect of natural concern. Due to their eco-accommodating nature broad looks into are going ahead to create different biodegradable polymers as a substitute for petrochemical based polymers. These biopolymers are huge macromolecules made out of single, repeating monomer units. They are of high molecular weight and their material attributes fluctuate as per the idea of their monomer piece. Their applications go from being utilized as a part of the packaging business, synthetic industry, agriculture and medicine. Thinking about these realities, expansive scale production of these biodegradable polymers and their broad utilize is basic both to guarantee elective wellsprings of plastic and furthermore for the earth.

These biodegradable polymers can be categorised into two unique classes' i.e. natural and synthetic polymers. The previous are acquired from natural sources and the later require chemical synthesis. Natural polymers can be additionally ordered into four unique classes relying upon their sources including agricultural, animal, marine and microbial sources. Those that are gotten from the agricultural sources include polysaccharides, proteins and lipids which thusly include starches, lignocellulose items, for example, pulp and pectin. Biopolymers got from animal sources are gelatine and collagen while marine sources can deliver chitin which is prepared into chitosan. Polymers got from the microbial sources include polyhydroxyalkanoates (PHA) and polylactic acid (PLA) (P. Basnett et al., 2010).

Polyhydroxyalkanoates are produced entirely by microbial fermentation while polylactic acid is partially synthesised. The monomer, lactic acid, is produced by microbial fermentation and after that polymerised utilizing chemical catalysis. Various bacteria accumulate polyhydroxy alkanoates (PHAs) as intracellular carbon reserves when supplement inadequacies happen. Natural polymers can be totally degraded by the microorganisms and degradation involves enzymatic scission of the polymer chain. The truncated polymer chain is later processed. Synthetic polymers then again can be combined utilizing bio derived monomers or synthetic monomers (precursors) derived from petroleum products (Kolybaba et al., 2003). The biopolymers, which are microbially created polyesters, have similar thermoplastic and water-resistant qualities as synthetic plastics.

Polymer materials are solid, non-metallic compounds of high molecular weights (Callister et al., 1999). An assortment of materials (both renewable and non-renewable) is utilized as feedstock hotspots for present day plastic materials. Plastics that are shaped from non-renewable feed stocks are generally petroleum-based and reinforced by glass or carbon fibres (Williams et al., 2000) Renewable resource feed stocks incorporate microbially-developed polymers and those separated from starch. It is possible to fortify such materials with natural fibres, from plants such as flax, jute, hemp, and other cellulose sources (Bismarck et al., 2002).

Biodegradable polymers are classified into two groups. The main groups are (i) the Agro-polymers (polysaccharides, proteins, etc.) and (ii) the Bio polyesters (biodegradable polyesters) such as polylactic acid (PLA), polyhydroxyalkanoate (PHA), aromatic and aliphatic copolyesters (Avérous et al., 2008)

Microbial polymers

Microbial polymers are produced by a range of microorganisms under different development conditions. Under pressure conditions, for example, abundance carbon and restricting nitrogen, Polyhydroxyalkanoates are produced by the microorganisms as storage molecules. Lactic acid is delivered by the gathering of lactic acid creating microbes by fermenting hexoses into lactic acid. For the chemical synthesis of PLA this decontaminated lactic acid is utilized as the precursor. To accomplish efficient generation of these biopolymers in a modern scale enterprises have been utilizing cheap carbon sources.

polyhydroxyalkanotes (PHA)

Polyhydroxyalkanoates (PHAs) include a huge class of polyesters that are synthesized by numerous microbes as an intracellular carbon and energy compound when carbon is abundant; however different supplements (e.g. nitrogen, phosphorus) are restricting. PHAs can be arranged into two primary types, short chain length PHAs (SCL-PHAs) that have C3-C5 hydroxy acids as monomers and medium chain length PHAs (MCL-PHAs) that have C6-C16 hydroxy acids as monomers. The mechanical properties of these PHAs fluctuate from being very weak to amazingly elastomeric. The organization of the polymer integrated is directed by the bacterial strain being used and the carbon source used to build up the microorganisms. From now on, depending upon the possibility of the biomedical application, one can bioengineer the generation of a PHA with suitable material properties. SCL-PHAs are exceedingly crystalline, fragile and hardened while MCL-PHAs are elastomers with low crystallinity and low glass transition temperature. The length of the side chain and its functional group extensively influence the properties of the bio plastic, e.g., melting point, glass transition temperature, and crystallinity (stiffness/flexibility). Likewise, the average molecular weight and the molecular weight distribution are reliant on the carbon source. Chemical treatment (acetylation) of the fibres is performed in order to adjust the surface properties, without changing the fibre structure and morphology (Frisoni et al., 2001). Bledzki et al. inferred that fibres that have been altogether dried before being added to the matrix show improved adhesion instead of fibres with higher moisture content (Bledzki et al., 1999). Research has demonstrated that polyvinyl alcohol is a suitable polymer to use as a network in regular fibre strengthened composites, as it is exceptionally polar and biodegradable (Chiellini et al., 2001). The general structure of Polyhydroxyalkanotes is appeared in Figure 1 (Valappil et al., 2014).

The PHA biosynthetic pathways

Many microorganisms synthesize PHA in the form of granules in the bacterial cell cytoplasm. Under microscope, a protein monolayer is found on the surface of PHA granules (Figure 2) (Manfred et al,. 2001). To remove the protein layer the bacterial cell needs to be ruptured.

There are three suitable metabolic pathways for the synthesis of PHA shown in the Figure 3 (Philip et al., 2006).

Cupriavidus necator is the most extensively studied microorganism for the cost-effective production of PHA. Two molecules of acetyl-CoA are condensed by “-ketothiolase (PhaA) to form acetoacetyl-CoA. Subsequently, NADPH-dependent acetoacetyl-CoA reductase (PhaB) catalyzes the reduction of acetoacetyl-CoA to the (R)-isomer of 3-hydroxybutyryl-CoA which is then polymerized into P(3HB) by the PHA synthase (PhaC).

Another organism *Pseudomonas aeruginosa* uses fatty acid ß-oxidation pathway for the production of hydroxyacyl substrates from carbon sources such as fatty acids. PHA is then polymerized by these hydroxyacyl substrates. This reaction is catalysed by the PHA synthase enzyme.

Some organisms use fatty acid de novo pathway when sugar is used as the carbon source. The enzyme acyl-ACP-CoA transacylase (phaG) converts the (R)-3-hydroxyacyl intermediates from the fatty acid biosynthetic pathway from their acyl carrier protein (ACP) form to the CoA form. phaG acts as the link between fatty acid synthesis pathway and PHA biosynthesis pathway.

SCL-PHAS

In 1927, Lemoigne first discovered short chain length polyhydroxyalkanoate i.e. poly(3-hydroxybutyrate) or P(3HB), a member of the PHA family, in Bacillus magisterium (Lemoigne et al., 1927). Now-a-days various other bacterial strains including soil bacteria, algae and also recombinant strains are used for their production. P(3HB) is almost 80% crystalline and has an extremely high melting point of 173-180°C. These polymers are stiff and thermoplastic in nature, hence are not easily processed. P(3HB) is degraded by the hydrolytic cleavage of the ester bonds resulting in surface erosion.

P(3hb) production

The most common SCL monomer in SCL-PHA polymers is 3-hydroxybutyrate (3HB). PHB can be produced from a number of different carbon sources. Generally, glucose is metabolized via glycolysis to produce pyruvate. For aerobic growth, pyruvate is converted to acetyl-CoA and is used to make reducing equivalents through the tricarboxylic acid cycle.

The production of P(3HB) was carried out by El-Sayed and co-workers using batch, fed batch and two stage fermentation processes (El-Sayed et al., 2003). They concluded that the two-stage batch culture was the most favourable method for the production of P(3HB) by Cupriavidus necator. Akhtar and Pouton have determined the glass transition temperature (Tg) and the melting temperature (Tm) of P(3HB) to be -5 ± 20ºC and 160ºC-180ºC respectively.

One of the most significant developments in the biosynthetic pathways for specialized PHA polymers from nonrelated carbon

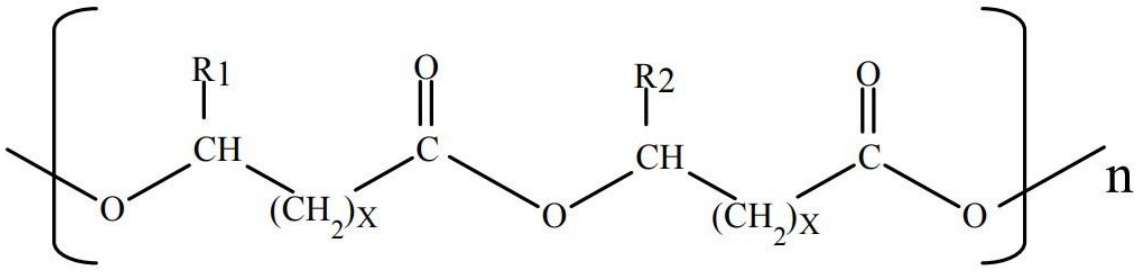

Figure 1. The general structure of polyhydroxyalkanoates (x = 1, 2, 3; n = 100-30000; R1, R2 = alkyl groups, C1-C13).

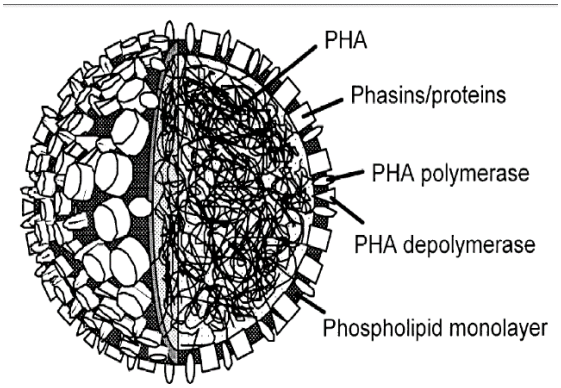

Figure 2. Scheme of a PHB granule. The core consists of PHA polymers that are covered by a lipid monolayer with integrated proteins. The lipid monolayer points with the hydrophobic side to the core. The integrated proteins consist of PHA polymerase, depolymerase, structural proteins (phasins), and proteins of unknown function

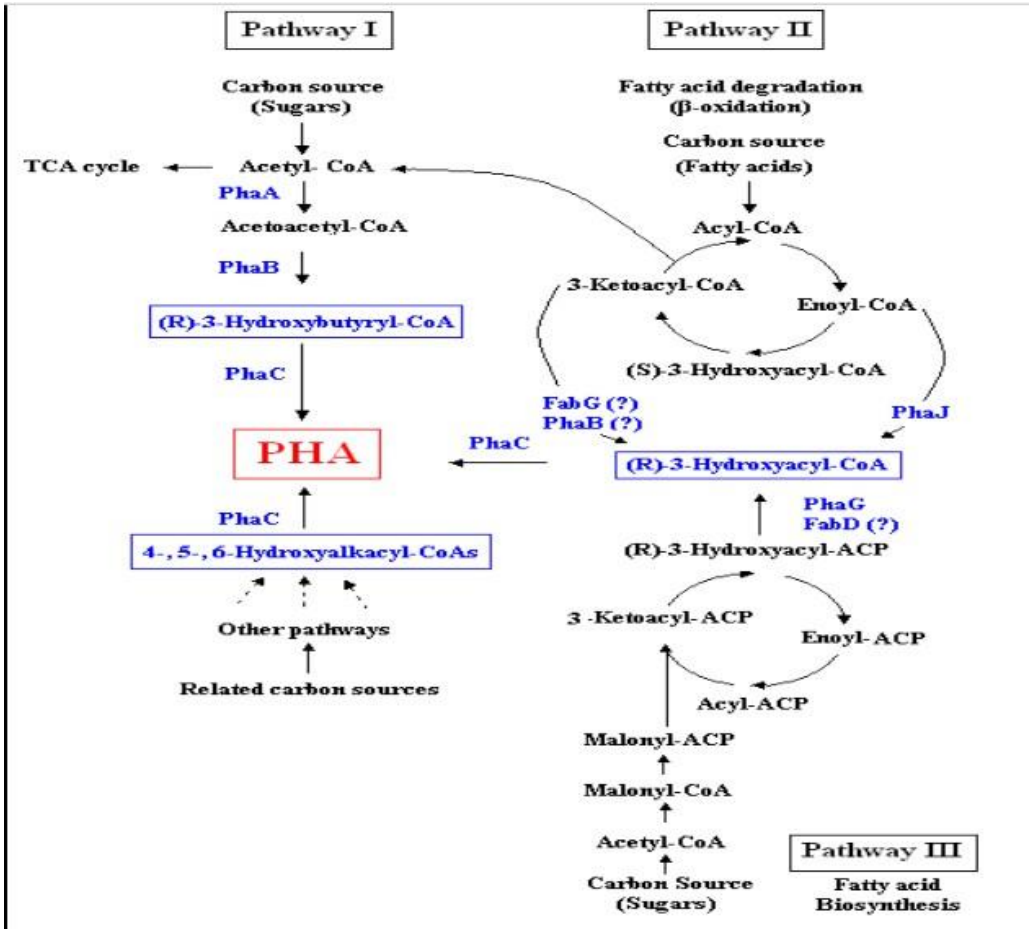

Figure 3. The three pathways for the production of PHA from different organisms.

sources is the production of polylactide-co-3hydroxybutyrate (P3HB) by Taguchi and co-workers (Taguchi et al., 1999). The synthetic metabolic pathway to convert pyruvate to lactate via lactate dehydrogenase (LDH) and the subsequent conversion by propionyl-CoA transferase (PCT) of lactate to lactyl-CoA, a substrate for engineered PHA synthases to copolymerize with 3HB monomers produced from the PhaAB pathway. The first reaction is catalysed by beta-ketothiolase (PhaA) to convert two molecules of acetyl-coA to acetoacetyl-CoA. This reaction is followed by the reduction of acetoacetyl-CoA to (R)-3-hydroxybutyryl-CoA by the reductase PhaB. Finally, 3-hydroxybutyryl-CoA is polymerized into PHB by PHA synthase. P(3HB-co-3HV) copolymers have a variety of uses as single use, bulk-commodity plastics in the marine environment, and in biomedical applications. Normally, P(3HB-co-3HV) is synthesized in bacteria grown on a mixture of glucose and propionate.

Medium-chain length PHAs (mcl-PHA)

The mcl-PHA is comprised of monomers having 6 to 14 carbon atoms. These include 3-hydroxyhexanoate, 3-octanoate and 3-hydroxydecanoate. P. oleovorans and P. putida produce mcl PHA through β-oxidation, but in contrast to P. putida, P.

oleovorans cannot produce PHA when grown on fructose, glucose, and glycerol, or substrates that require fatty acid de novo synthesis.

Biosynthetic Pathways for the Production of MCL PHA

Fatty acid biosynthesis develops unsaturated fats by the addition of two carbons for each cycle through acyl carrier protein (ACP) connected intermediates. Co-articulation of 3-ketoacyl-acyl carrier protein synthaseIII genes (fabH), conveying site-specific transformations which changed their substrate specificity with different PHA synthase genes prompted the generation of SCL-MCL PHA copolymer in recombinant E. coli developed within the site of excess glucose. Genetically modified thioesterases were fit for delivering MCL PHA monomers by means of the β-oxidation pathway, even in microorganisms developed on random carbon sources. This pathway requires the deletion of genes in the host strain encoding catalysts associated with the β-oxidation pathway (fadR and fadB) in order to be effective. PhaG was initially identified as an acyl-ACP: CoA transacylase. To recognize the movement of PhaG monomer-supply pathway, recombinant E. coli strains required the presence of the fatty acid biosynthesis inhibitor triclosan all together for the strain to be powerful as a MCL-PHA monomer provider. Nonetheless, late examinations have demonstrated that PhaG really acts as a hydroxyacyl-ACP specific thioesterase and the extra articulation of acyl-CoA synthetase (AlkK) will initiate 3-hydroxy acid intermediates created by PhaG for PHA biosynthesis. The identification of this "missing link" has opened the entryway for future examinations to enhance the creation of MCL-PHA monomer supply from the fatty acid biosynthetic pathway through chemical advancement strategies. The pervasiveness of fatty acid biosynthesis pathways in all life forms makes the fatty acid biosynthesis inferred generation of SCL and MCL monomers appealing, since this framework might be exchanged to photosynthetic creatures to additionally diminish production costs by using CO2 rather than processed plant oils or sugars as carbon sources.

POLYLACTIC ACID

PLA belongs to the group of aliphatic polyesters usually produced using - hydroxy acids, which likewise includes polyglycolic acid (PGA). It is one of few polymers in which the stereo chemical structure can easily be modified by polymerizing a controlled blend of l and d isomers to yield high molecular weight and amorphous or semi-crystalline polymers (Christopher et al., 2012). PLA is viewed both as biodegradable and as biocompatible in contact with living tissues (e.g., for biomedical applications, for example, implants, sutures, drug encapsulation, and so forth). PLA can be degraded by abiotic degradation (i.e. basic hydrolysis of the ester bond without requiring the presence of catalysts). Amid the biodegradation procedure, and in a second step, the compounds debase the residual oligomers till final mineralization (biotic degradation). As long as the fundamental monomers (lactic acid) are delivered from renewable sources (carbohydrates) by fermentation, PLA conforms to the rising overall idea of feasible improvement and is classified as a domain amicable material.

SYNTHESIS OF PLA

The synthesis of PLA is a multistep process which starts from the production of lactic acid, condensation of lactic acid through fermentation processes and ends with its polymerization as shown in Figure 4 (Avérous et al., (2008); Christopher et al., 2012). An intermediate step is often seen during the formation of the lactide. There are three main routes for synthesis of PLA. Lactic acid is polymerized to yield a low molecular weight, brittle polymer, which, for the most part, is unusable, unless external coupling agents are employed to increase its chains length. Second route is the azeotropic dehydrative condensation of lactic acid. It can yield high molecular weight PLA without the use of chain extenders or special adjuvants. The third and main process is ring-opening polymerization (ROP) of lactide to obtain high molecular weight PLA, patented by Cargill (US) (Sodergard et al., (2002); Averous et al., 2010). Finally, lactic acid units can be part of a more complex macromolecular architecture as in copolymers.

Mechanical properties of lactic acid-based polymers vary from being flexible to stiff and high strength materials. PLA is a hydrophobic semi crystalline polymer and has a glass transition temperature TG, of 55ºC and a melting temperature, Tm of about 180ºC. The tensile strength of PLA is 32.22 MPa and its elongation to break is 30.7%. The melt enthalpy of the 100% pure PLA has been estimated to be 93 J/g. The solubility of these lactic acid based polymers depend on the molar mass, degree of crystallinity and the monomers that make up the polymer.

PHA and PLA are both considered synthetic polymers, as they are not found in nature. However, they are wholly biodegradable (Stevens et al., 2003).

GENERAL APPLICATIONS OF NATURAL POLYMERS

Biodegradable packaging materials have been utilized in order to diminish the volume of inert materials at present being discarded

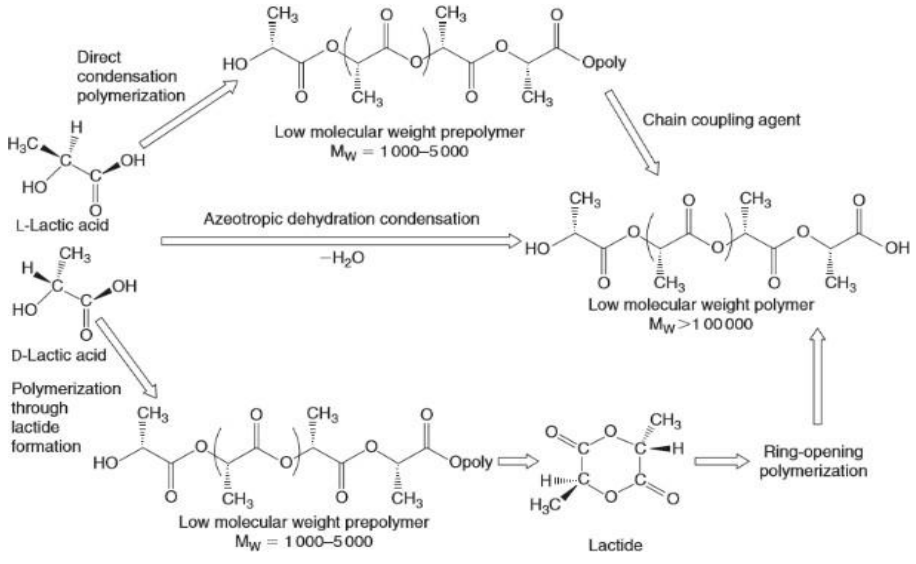

Figure 4. Synthesis pathways of high molecular PLAs.

in landfills, possessing rare accessible space (Bastioli et al., 1998). It is evaluated that 41% of plastics are utilized as a part of packaging, and that half of that volume is utilized to pack food products.

From an agrarian outlook, compartments, for example, biodegradable plant pots and disposable composting containers and sacks are new zones of intrigue. Li et al. presumed that the utilization of an unmistakable plastic mulch cover instantly following seeding expands the yield of spring wheat if utilized for less than 40 days (Li et al., 2009). Biopolymers which are compostable are imperative, as they may supplement the present nutrient cycle in the soil where the remainders are added.

Bio based cars are lighter, settling on them a more temperate decision for customers, as fuel costs are decreased. Natural fibres are substituted for glass fibres as reinforcement materials in plastic parts of automobiles and commercial vehicles (Lammers et al., 2002).Biopolymer materials are as of now consolidated into glues, paints, motor oils, and construction materials (Fomin et al., 2011)

The therapeutic world is continually changing, and thusly the materials utilized by it likewise observe repetitive modifications. The biopolymers utilized as a part of medical applications must be compatible with the tissue they are found in and may or may not be expected to break down after a given time period. Mukhopadhyay reported that researchers working in tissue engineering are attempting to develop organs from polymeric materials, which are fit for transplantation into humans (Mukhopadhyay et al., 2002). Artificial bone material adheres and integrates onto bone in the human body. Another application for biopolymers is in controlled release delivery of medications. The bioactive material releases medication at a rate determined by its enzymatic degradation (Sakiyama et al., 2001). PLA materials were developed for medical devices such as resorb able screws, sutures, and pins.

The attraction of biopolymers in all of these areas is their derivation from renewable sources, slowing the depletion of limited fossil fuel stores.

ROLE OF BIODEGRADABLE POLYMERS IN CARDIAC STENT DEVELOPMENT

Heart disease is the greatest enemy of world now-a-days as consistently because of lethal cardiovascular ailment loads of individuals die. Coronary artery disease (CAD) is one of the cardiovascular infections in which the artery gets clogged or narrowed because of the accumulation of cholesterol, fats and different components of the blood as appeared in Figures 5-7 (Kulick et al., 1990). Most of the time, deposition of platelets in veins diminishes the lumen measurement and influences the blood stream to the cardiovascular muscle which makes insufficient supply of oxygen rich blood to the heart, prompting heart attack. This major issue can be overcome by a strategy called Angioplasty in which arteries and veins are enlarged. A catheter with an inflatable at its tip is coordinated to the blocked area of the vein through the groin or arm. The whole method is observed by X-ray screening. On reaching the site of blockage, the balloon is inflated and a stent is put in the artery which holds the narrowed blood vessel because of which the fatty deposits are squashed (NIH 2010). This permits normal blood flow into the heart.

Restenosis

In few cases following 3 to a half year of Angioplasty, reoccurrence of blockage in the artery has been observed after stent placement called as restenosis. The three principle factors that cause restenosis: (a) injury caused to the blood vessel amid stent replacement (b) interaction occurring between the components of the blood and stent material which in some cases prompts an inflammatory reaction and (c) endothelial cell expansion caused because of low local wall shear stress (Nouyrigat et al., 2009).

The growth rate of the endothelial cells is controlled by discharging substances, for example, nitric acid and thrombomodulin. At the point when the wall shear pressure is high, significant amount of nitric acid is discharged which restrains the growth of endothelial cells while low wall shear pressure prompts the increased production of thrombomodulin and diminished generation of nitric acid. Subsequently, cell expansion occurs prompting restenosis (Nouyrigat et al., 2009).

BIODEGRADABLE DRUG ELUTING STENTS

Stents are scaffolds that are placed in the coronary artery to recover the shape of narrowed or diseased arteries caused due to accumulation of fatty deposits, cholesterol and other components of the blood. The two most important functions of a stent are to allow normal blood flow and to prevent restenosis.

Stack et al. at Duke University developed the first biodegradable stent and implanted it in animals (Stack et al., 1998). A polymer of poly-l-lactide was used for this prototype stent. The stent was almost completely degraded by 9 months.

Lincoff et al. demonstrated that poly-l-lactic acid (PLLA) with a low molecular mass (≈80 kDa) is associated with an intense inflammatory reaction, whereas a minimal inflammatory reaction occurs with implants that are coated with high-molecular-mass (≈321 kDa) PLLA (Lincoff et al., 2003).

Discrepancies exist when evaluations of these stents are performed in different animal models. In dogs, minimal tissue growth occurs, whereas in a pig model, marked cellular proliferation occurs.

Yamawaki et al were the first to incorporate an ant proliferative agent into the high-molecular-weight PLLA Igaki-Tamai stent (Yamawaki et al., 1998). Prostheses loaded with a compound that inhibits the activity of tyrosine kinases were implanted in a pig model. These authors showed that neointimal formation was significantly less at the sites where the PLLA stent was loaded with the specific inhibitor compared with sites treated with the same stent loaded with an inactive compound.

The availability of a device that combines the advantage of new-generation DES, in terms of reduction of restenosis and target-lesion revascularization (TLR), with the long term safety of bare-metal stents (BMS), regarding the risk of late stent thrombosis (ST), is highly attractive. It is well known that chronic inflammation to components of the permanent polymer represents an important factor associated with an increased risk of late DES failure and ST. Hypersensitivity reactions to the polymers may lead to delayed vessel healing and stent coverage by non-functional endothelium, factors implied in the main drawbacks of first-generation DES, such as stent thrombosis, restenotic late catch-up and vessel remodelling. To overcome these limitations, biocompatible and biodegradable polymers have been developed in the context of newer generation DES (Attizzani et al., (2014); Kuramitsu et al., 2016).

According to Zidar et al., the following are the characteristics of an ideal stent (Zidar et al., 1994)

a) They should be biodegradable in nature as this eliminates the need to remove the stent from the treatment site since they degrade in the body.

b) They should be flexible in nature to facilitate insertion.

c) They should possess mechanical properties such as high elasticity, high tensile strength, self-expandability, high ductility (to prevent deformation during expansion) and high radial strength (to prevent recoiling after the placement) to perform the function.

d) They should be able to release drugs such as rapamycin (immunosuppressant), or paclitaxel (mitotic inhibitor) or tranilast (anti-allergy) or heparin (anti-coagulant) at the treatment site to prevent restenosis.

A biodegradable stent loaded with the anti-restenosis drug minimizes the systemic toxic effects, facilitates the healing of the injured vessel caused due to the stent implantation and most importantly prevents restenosis. Moreover they are less obtrusive than metal stents.

The polymeric controlled release systems have been developed to introduce a new concept in drug administration to treat numerous diseases. The purpose of controlled release systems is to maintain an adequate drug concentration in the blood or in target tissues at a desired value as long as possible and, for this, they are able to control drug release rate (Pillai et al., 2001). Biodegradable polymers have been used in controlled drug delivery for many years as a means of prolonging the action of therapeutic agents in the body, without the need to remove the device after treatment (Domb et al., 2003). The significant feature of current biodegradable devices and coatings is that they provide a continuous drug release over an extended period of time. Optimized pharmacokinetic-pharmacodynamics effects of drugs is a prerequisite for a given extended drug release device to achieve favourable biological response. The drug release profile can be programmed to meet specific requirements by optimizing the composition of formulations, processing parameters such as coating level, drug-polymer ratio and type and amount of polymer-plasticizer utilized (Okarter et al., (2000); Shao et al., 2002). The ideal goal for any drug eluting device is to deliver the therapeutic agent of high efficacy at the right time to the desired location with a concentration high enough over a sufficiently long period. With targeted controlled drug delivery, combination products have already found applications in various areas of cardiovascular disease, diabetes, orthopaedics and cancer (Dubin et al., 2004). Using novel controlled release formulations, drug eluting stents (DES) were developed to target post angioplasty complications. They revolutionized the field of interventional cardiology by proving safety and efficacy in prevention of restenosis of coronary arteries using local drug delivery in many clinical trials (Colombo et al., (2003); Moussa et al., 2004).

Controlled release (CR) of drugs can be achieved by incorporating them either in dissolved or dispersed form in polymers (Wise et al., 2000). Depending on the final desired elution profile, these systems can be tailored to deliver the drug at a constant rate, in pulsatile manner, in the form of extended release and in other forms. Stent based delivery systems require a supply of anti-proliferative, anti-inflammatory, anti-thrombotic or pro-healing drugs at a programmable rate to maintain sufficient arterial drug concentrations to avoid excess cell growth with no toxic effects. The optimal release profile should be such that the concentration of drug is at any time sufficient to inhibit the proliferation of smooth muscle cells without influencing the re-endothelialisation process of the endothelial wall (Deconinck et al., 2008). The arterial drug dose and release kinetics are critical parameters that should be studied thoroughly to ensure device safety and efficacy (Balakrishnan et al., (2007); Prabhu et al., 2006).

MECHANISMS OF DRUG RELEASE KINETICS FOR CORONARY STENT

Elution kinetics for the majority of the DES currently investigated can be explained by diffusion. These systems can be classified as: (1) Monolithic devices in which the therapeutic agent is dispersed in a polymer matrix and its release is controlled by diffusion through the matrix; and (2) Reservoir systems (membrane controlled devices), in which the active agent is contained in a core that is surrounded by a thin polymer membrane and release to the surrounding environment occurs by diffusion through the rate-controlling membrane. Both of the systems have been utilized practically and DES based on this scheme has proven their safety and efficacy in many clinical trials (Kamath et al., (2006); Leon et al., 2003).

In monolithic systems, the release rate depends on initial drug concentration within the polymeric matrix. If the drug concentration is below the solubility limit in the matrix, then diffusion through the matrix limits the release rate and, if the drug concentration is above the solubility limit in the matrix, then drug dissolution in the polymer matrix limits the release rate. For reservoir systems, the drug release rate remains constant, which results in a zero order drug elution profile at the steady state and deviations in release rate can be recognized as an initial burst or time lag in drug release.

While the diffusion controlled release mechanism is adequate for stent systems that incorporate non-biodegradable durable polymers, regulated release profiles can be achieved by using biodegradable polymers. Examples of such polymers are polylactide, polyglycolide, polylactide-co-glycolide, polyhydroxybutyrate, hyaluronic acid, polycaprolactone, polyortho ester (Pan et al., (2006); Raval et al., 2007).The property by which these polymers undergo hydrolytic and enzymatic degradation when exposed to biological fluid makes them potential candidates for controlled drug delivery where polymer can be degraded, absorbed or excreted from a biological environment (Schliecker et al., (2003); Sun et al., 2006). Thus, drug release from these systems can be achieved by: (1) diffusion of drug from the polymeric matrix, (2) dissolution of drug into the release medium; and (3) biodegradation of polymeric chains. By careful optimization of the drug-polymer ratio (Kamath et al., 2006), drug density, drug-polymer selection, physical dimensions of the coated film and process parameters, adequate control over elution rate can be achieved (Finkelstein et al., 2003).

During studies on controlled elution of paclitaxel using a blend of biodegradable polymers from the class of polylactides and co-polymers of polylactide-co-glycolide, it was observed that adequate control over drug release could be attained by coating the stent in multiple layers (Raval et al., 2007). Each stereochemistry layer provides a different release rate depending on the composition of the respective layer and properties of the incorporated biodegradable polymers. Further research using similar biodegradable polymers revealed the fact that the initial rate of release was high compared to the later stage of drug release in simulated biological fluid (Kothwala et al., 2006).

Current experience with DES and a growing understanding of restenosis mechanisms confirm the short term benefits of DES surface coatings. However, long term complications such as incomplete drug elution, a suboptimal drug elution rate, delayed arterial healing, late stent thrombosis and hypersensitivity to the polymeric coatings remain an issue (Baim et al (2007); Finn et al.,2007). The findings have triggered the design and evolution of the next generation of coatings and novel coating strategies.

THE PRESENT HUMAN STUDY

Tamai et al provided the first report on the immediate and 6-month results after the implantation of a biodegradable PLLA stent in humans. This biodegradable stent combines the features of a thermal self-expandable and a balloon expandable stent. Initially, the stent auto-expands in response to the heat transmitted by a delivery balloon inflated with a 70°C contrast-water mixture

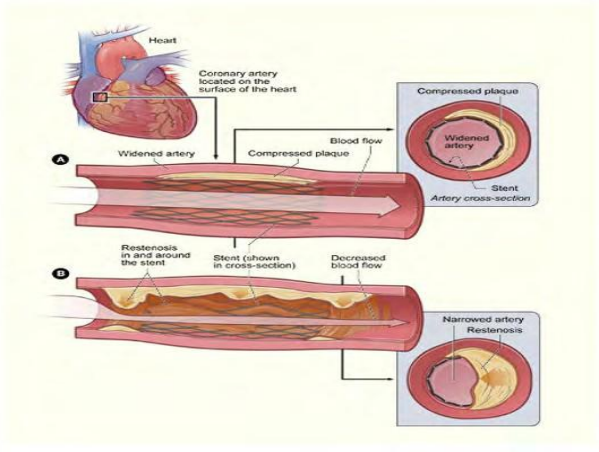

Figure 5. Coronary artery blocked by fatty deposits and blood clot

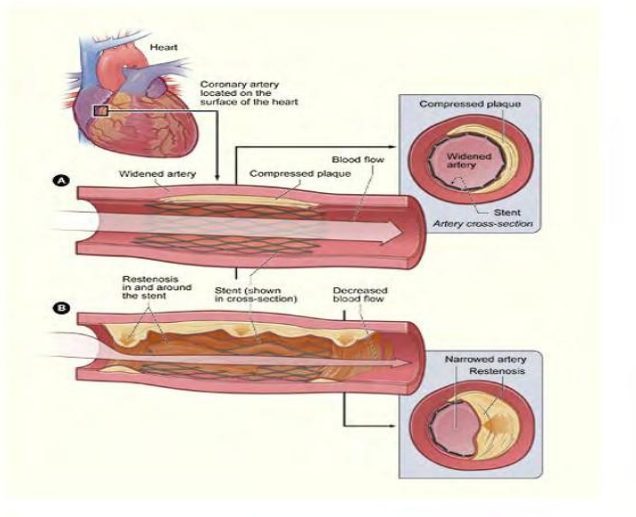

Figure 6. Angioplasty, a process where a catheter with an inflatable balloon carrying a stent is placed in the blocked coronary artery to widen the artery.

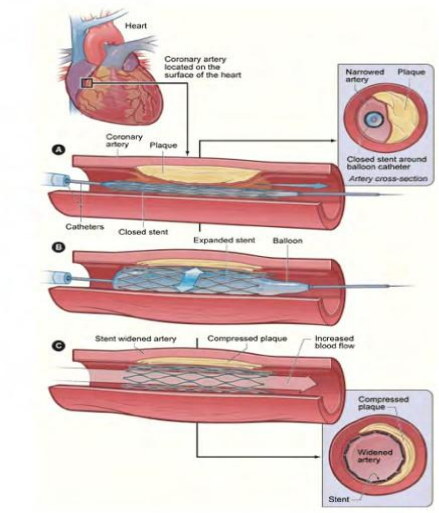

Figure 7. In stent restenosis, the reoccurrence of artery blockage due to lesions created during the angioplasty.

(50°C at the balloon site). Subsequent expansion is obtained with inflation at a moderate to high pressure (6 to 14 atm). This stent will continue to expand to its nominal size in the following 20 to 30 minutes at 37°C; it maintains a radial strength similar to or higher than that of the Palmaz-Schatz stent (Tamai et al., 2002).

The most important and unique innovation done by Tamai and other authors is the change in stent design from a knitted pattern to a zig zag pattern which reduced the amount of initial thrombus deposition and tissue proliferation. Tamai et al report on the first 15 patients treated with the Igaki-Tamai high-molecular-mass PLLA self-expandable stent. A total of 25 stents were electively and successfully implanted in 19 lesions (Tamai et al., 2002). The authors provide clinical and angiographic follow-up data at 1 day, 3 months, and 6 months. The small number of patients and lesions treated should not elicit any conclusions concerning the 10.5% restenosis rate per lesion at the 6-month angiographic examination. Nevertheless, the presence of a loss index of 0.48 at 6 months is a very encouraging finding; it shows, for the first time in human coronary arteries, that this type of biodegradable stent may not be associated with more pronounced intimal hyperplasia than stainless steel stents.

It is interesting to note that the continuous self-expansion of the stent progresses up to the third month after implantation. After the third month, no further stent expansion occurs. The authors elaborate on this result by stating that this type of stent does not stimulate intimal hyperplasia within the stent between 3 and 6 months.

A possible concern is related to the heat necessary to provide the rapid expansion of this stent. Even mild short-term temperature elevation (65°C to 75°C for few seconds) can cause necrosis of the arterial wall. An extended follow-up period with intravascular ultrasound evaluation will be necessary to answer this critical question. In this respect, the report seems not yet complete and fully demonstrative.

To effectively impact tissue growth, it may be necessary to add specific ant proliferative compounds to this biodegradable stent. The encouraging results after the implantation of a PLLA biodegradable stent loaded with tyrosine kinase inhibitor in pigs remain to be confirmed in humans.

Finally, Ye et al demonstrated the successful transfer and expression of a nuclear-localizing β-Gal reporter gene in cells in the arterial wall of rabbits after the implantation of biodegradable polymer stents (PLLA/polycaprolactone blends) impregnated with a recombinant adenovirus carrying that gene (Ye et al., 1998). The possibility of transferring genes that code key proteins in the central regulatory pathways of cell proliferation inside the cells of the arterial wall using biodegradable stents as vehicles is exciting. Regardless of which agent (gene or drug) will finally conquer restenosis, a biodegradable stent remains the optimal vehicle for such delivery.

Several recent studies have suggested that clinical outcomes in patients treated with everolimus-eluting bioresorbable scaffolds for coronary artery revascularization are within the range for non-inferiority when compared with drug-eluting metallic stents (Metzger et al., (2015); Dudek et al., (2015); Tanabe et al., 2015).

This work is a resulted from the traditional view of stents, which considers them permanent prostheses able to withstand decay because they replace a missing part of the body. This effort represents the first move toward a new concept of coronary stenting: “fulfil the mission (with possible local drug or gene delivery) and step away.”

CONCLUSION

Recombinant production of molecules such as PHAs will undoubtedly thrive on the enormous biological diversity of nature, where novel protein activities can be obtained from exotic places, while gene cloning becomes less and less of a technological hurdle. Biodegradable polymers are likely to play a significant role in building an eco-friendly environment by replacing the widely used non-biodegradable synthetic plastics because the level of biodegradation may be tailored to specific needs. However, to make inroads into the thermoplastic dominated market, economical production of the biodegradable polymers is a must. Microbially grown plastics are scientifically sound, and a novel idea, but the infrastructure needed to commercially expand their use is still costly, and inconvenient to develop. Reduction in the cost of production, resulting in the competitive price of the biodegradable polymers will broaden their range of application. The key properties of these biopolymers such as biodegradability and biocompatibility have made it feasible to envisage the extensive use of these biopolymers in the biomedical field. Their role in cardiac stent development is significant. It is impossible to predict the future with certainty but the data revealed from the studies so far have been very promising. Hence, Time is of the essence for biodegradable polymer development, as society's current views on environmental responsibility and biomedical uses make this an ideal time for further growth of biopolymers.

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