Extraction and polymerization of lactic acid to polylactic acid

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Abstract

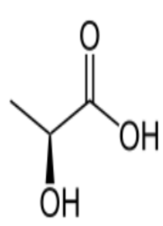
Polylactic acid is one of the most famous biodegradable polymers, because it is eco-friendly, can be produced from renewable sources. It has been studied extensively because of its various applications in biomedical field. PLA can be used in human body. There are various methods of synthesizing PLA such as ring opening polymerization, melt polycondensation, microwave irradiation etc. Lactic acid can be produced by fermentation of sugar and various other renewable raw materials. In this review paper, different polymerization reactions of PLA from lactic acid is discussed. Also important applications of PLA such as drug delivery system, implants, tissue engineering etc are outlined.

Introduction

Lactic acid is an organic acid found in milk and other food products. Lactic acid is used in food industries as a preservative, flavour enhancer, and to adjust the acidic level. It is also used in pharmaceuticals, textiles, cosmetics and chemical industries. The demand for lactic acid has become huge because of its potential ability to produce poly lactic acid (PLA). Generally they can be produced biologically or by chemical synthesis. Musashino Chemical Laboratory, ltd, in Tokyo, Japan is the sole producer of synthetic LA, producing approximately 7,000 metric tons per year (Biddy et al.2016; Musashino Chemical Laboratory, 2017).

Poly Lactic Acid (PLA) is classified as eco-friendly polyester because it is biodegradable as well as renewable. The attractive price and commercial availability of lactic acid are the most important reasons for PLA development. Among the biopolymers that are being used in industries nowadays, PLA is considered to be the best. First PLA with a low molecular weight was synthesized by Carothers in 1932. Later, Du Pont worked on creating a high molecular weight PLA, which patented in 1954. Biodegradable polymers are more famous in medical applications because they are more advantageous than the non-biodegradable ones. PLA is also considered because of its low cost as compared to other traditional resources. In this paper we are aiming to discuss the properties of lactic acid and poly lactic acid, and compare various methods of the production of PLA from lactic acid.

1. Chemical Properties of Lactic Acid



L-Lactic Acid

Molecular formula	$C_3H_6O_3$
Molar mass	90.08 g/mol
Density	1.209 g/mL
Melting point	L: 53 °C D: 53 °C D/L: 16.8 °C
Boiling point	122 °C at 15 mmHg

2. Importance of Lactic Acid

Lactic acid is a hydrocarboxylic acid having various household and commercial applications. In food industries it is used as a flavouring agent, pH regulator, preservative, prevents spoilage of food. In pharmaceuticals it is used to obtain water soluble substances (lactates) from the insoluble ingredients. Also used for topical preparations to adjust the acidic level and also for its disinfectant properties.

The casein in fermented milk is curdled by lactic acid. In wine making, a bacterial process is carried out to convert the malic acid lactic acid. This malolactic fermentation is done by lactic acid bacteria (LAB). In cosmetics it is used as a moisturizer. It is used as a mordant in textile industries (Young-Jung Wee et al. 2006).Also used in leather tanning process. It is involved in the manufacturing of lacquers and inks.

3. Sources of Lactic Acid

Lactic acid can be derived using various raw materials such as-

3.1 *Sugarcane*

Due to the high cost it is less feasible to use. However the waste material from food industries or sugarcane mills can be used as a source to avoid environmental or economical issues.

3.2 *Starchy Materials*

Wheat, corn, maize, potato, rice, rye, barley etc are potential sources of lactic acid. Approximately 90% of lactic acid which is commercially available is produced by the submerged fermentation of corn.

3.3 *Whey*

It is a suitable raw material for the production of lactic acid, because it contains lactose, proteins, fats, water soluble vitamins, mineral salts, and other essential nutrients for the growth of microbes.

3.4 *Food Wastes*

It is a potential source of lactic acid production because it is mostly rich in carbohydrates, also being a helpful method in waste management.

3.5 *Glycerol*

It is a by-product of biodiesel production. The production of lactic acid from glycerol can be categorized into hydrothermal and heterogeneous catalysis method.

3.6 ***Microlage***

They are another potent raw material. They can grow almost everywhere, have a very short harvesting cycle (1-10 days) and have high sugar content (fermentable).

3.7 ***Lignocellulose Biomass***

It is also a promising source for lactic acid production. It can be used to obtain sugar solutions that could be exploited to produce lactic acid, by using the following steps- a) pre-treatment in order to break down the lignocellulosic structure b) hydrolysis with enzymes to depolymerise the lignocelluloses to fermentative sugars c) fermentation of sugar to lactic acid.

3.8 ***Sweet Sorghum Juice***

It can also be used as a raw material for lactic acid production by using downstream process.

4. Importance of Microbial Fermentation in Lactic Acid Synthesis

Microorganisms play an important role in the production of lactic acid. The microorganisms producing lactic acid can be categorized into bacteria, fungi, and yeast.

4.1 ***Bacteria***

Most of the industrial production of lactic acid is done by the use of lactic acid producing bacteria. They can produce lactic acid by anaerobic glycolysis with high yield. They are found in dairy products, meat and plants. Generally the optimal temperature is 5-45°C and optimal pH range for bacterial growth is 3.5-9.6. Depending on the end product of the fermentation process, the lactic acid bacteria are divided into 2 groups- homo fermentive and hetero fermentive. Homo fermentive LAB converts glucose into lactic acid by Embden-Mayerhof pathway. The main reason for the usage of lactic acid bacteria in industries is, they do not have harmful effects on health, also they have high acid tolerance.

4.2 ***Fungi***

Some fungal species like Rhizopus can use glucose to aerobically produce lactic acid, by the help of amylolactic enzymes present in them. Fungal fermentation is more favourable because of its low cost downstream process, less nutrients requirement, also the fungal biomass which is the by product of the process also becomes very easy, because it uses chemically defined medium. The main disadvantage of the fungal fermentation of lactic acid is that, the yield is reduced as the carbon is used for the production of by products alongwith lactic acid.The drawbacks of this process also includes the difficulty in mass transfer, which leads to low production rate.

4.3 ***Yeasts***

Every fermentation process requires abundant quantity of nutrients supply. Yeast is used as the key nutrient source in many fermentation processes. The main advantage is that, they can survive at a very low pH (1.5), preventing the regeneration of calcium lactate in mineral media. The yield of lactic acid production by use of wild type of yeasts is low. Genetically modified yeasts can successfully produce more lactic acid. Few genetically modified species used for this purpose are- *Saccharomyces, Candida, Pichia, Zygosaccharomyces.* The main disadvantage of using yeast is that it increases the cost of production. Wheat bran, rice bran, corn steep liquor etc could be used as alternatives for yeast.

5. Different Separation Strategies of Lactic Acid

There are several processes for the production of lactic acid-

5.1 ***Chemical Synthesis***

It produces a racemic mixture of lactic acid by using acetaldehyde as a starting material. Lactic acid (racemic) is then synthesized by reacting acetaldehyde with hydrogen cyanide, followed by hydrolysis of the resultant lactonitrile. While hydrolysing, ammonium chloride is formed as a by-product. Other substances could also be used as starting materials for this process, such as- vinyl acetate, glycerol etc.

5.2 ***Fermentation***

It is the most favourable process. About 90% of lactic acid is produced by fermentation (Joglekar et al. 2006). Low cost raw materials such as starchy materials are used, which is also renewable (Wang et al. 2010; Li et al. 2012; Nakano et al. 2005). Other raw materials such as sugarcane (Laepaiboon et al. 2010), whey (Tejayadi and Cheryan 1995;

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Kim et al. 2006; Li and Shahbazi 2006) etc are also used. Researches are going on to find ways to use lignocellulosic biomass as a carbohydrate source to produce lactic acid (Biddy et al. 2016).

5.3 *Neutralization and Precipitation of Salt with Acid*

In this process the calcium carbonate or calcium hydroxide is added in excess amount to the fermenter to neutralize the acid which is produced, pH is maintained around 5-6 and a calcium salt of lactic (calcium lactate) is produced. in this method, the fermentation broth is reacted with sulphuric acid, to precipitate the calcium sulphate (gypsum) which is then filtered. This filtrate contains free organic acid, which is evaporated to obtain pure lactic acid.

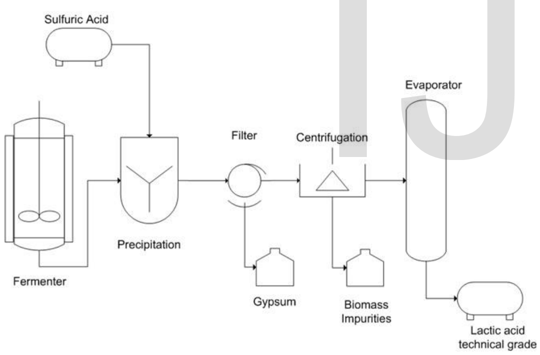


Fig. 1. General schematic for lactic acid recovery by precipitation

5.4 *Solvent Extraction or Liquid-Liquid Extraction*

It is an alternative to the classical precipitation process. In solvent extraction, solutes are removed from one liquid and transferred to a second liquid introducing a solvent. The separation is based on the difference in the solubility of the solutes in the two liquid phases. Few other factors which play an important role are extractant solubility, choice of solvent (chemically stable, renewable, less corrosive, low viscosity etc). Diluents are often used to enhance the extracting power of the solvent. Several studies have been done for the better solvent extraction, which are categorized as-

1. Conventional oxygen bearing hydrocarbons, such as octanol and methyl isobutyl ketone (MIBK).

2. Phosphorus bonded oxygen bearing solvents, such as tributyl phosphate.

3. High molecular weight aliphatic amines, such as dodecyl amine.

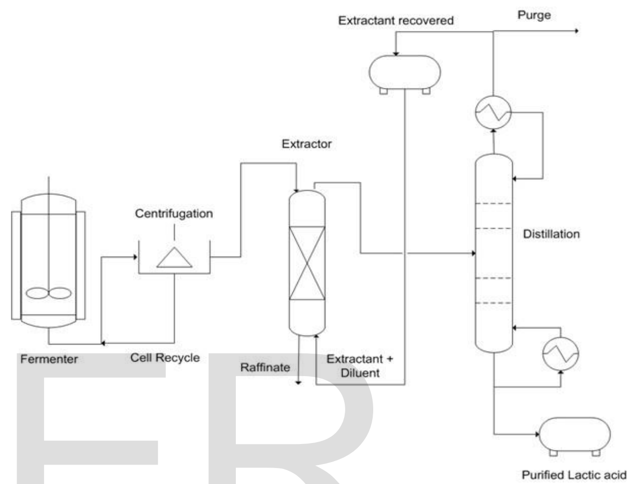


Fig. 2. General schematic for lactic acid recovery by solvent extraction

5.5 *Separation with Membranes*

This process is based on the transfer of solutes through semi-permeable membrane that separates two phases. Various chemical industries use this process such as water treatment plants, food industries, pharmaceuticals etc. The advantage of this process is its specificity and less power consumption. Since 1960 membrane separation process has been an alternative for lactic acid production. Michigan Biotechnology Institute (MBI) and Argonne National Laboratory (ANL) developed a process using double electrolysis which gives promising results. It uses electro dialysis desalting for the removal of multivalent cations, and to produce concentrated lactate salt. Ammonia is recycled in this process. This process is flexible enough depending on the market demand. Due to the usage of semi permeable membranes, the level of purity is very high. Although few limitations are there such as high cost of membranes, polarization, fouling etc). Hence, more research work should be done to make this process more useful.

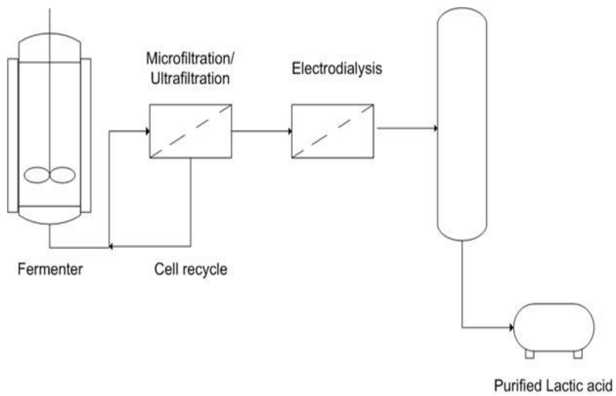


Fig. 3. General schematic for lactic acid recovery by membranes

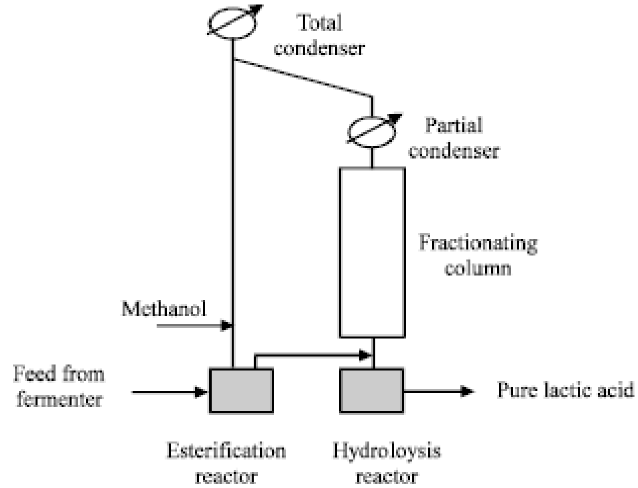


Fig.4: A conceptual block diagram for lactic acid recovery from the fermentation product (Choi and Hong 1999)

5.6 ***Distillation***

This technique was first applied by Schopmeyer and Arnold in 1944. In this process the crude lactic acid reacts with low boiling aliphatic alcohol (methanol) in presence of a catalyst (sulphuric acid). This process becomes difficult to use in industrial level because of the corrosion and problems in the separation. To overcome this problem, batch reactive distillation system was developed by Choi and Hong in 1999. They used the cation exchange resins, containing esterification and hydrolysis reactor, and a fractioning column (as shown in fig.4). The esterification reactor involves the esterification of crude lactic acid with methanol. The vapours of unreacted methanol, water and the product (methyl lactate) then pass through the fractioning column. Methyl lactate and water get condensed in the partial condenser because of their low volatility; and then flow down towards the hydrolysis reactor. Methanol and lactic acid are obtained by hydrolysis of methyl lactate.

The conventional method for lactic acid recovery is precipitation; but it is not well accepted in economical or environmental aspects, because the LA produced is of low quality. Unlike precipitation, solvent extraction does not produce a lot of waste. Although it has few limitations in large scale potential such as high cost, toxicity, large exchange area etc. Advancements in extractants have shown better results. Membrane based separation technique is highly selective; it has high level of purification and separation. It also has some disadvantages such as high of purification and separation. It also has some disadvantages such as high cost of membranes, polarization, fouling problems etc. Recovery of lactic acid by distillation (batch distillation) has been emphasized. As water removal increases with time, the percentage of free and total lactic acid also increases. The yield of the lactic acid increases (almost 95%) with the increase of weight of the catalyst.

What is Poly Lactic Acid

Lactic acid is the building block for poly lactic acid (PLA) synthesis. PLA is biodegradable aliphatic polyester. It was first synthesized by Wallace Carothers in 1932 (Lunt 1998) by heating lactic acid under vacuum by removal of condensed water. This PLA produced was of low molecular weight. Later high molecular weight PLA was produced by using lactic acid as raw material by the help of Ring Opening Polymerization (ROP). LA is a chiral molecule that exists in both L and D isomers which can be polymerized into pure poly-L-LA (PLLA), pure poly-D-LA (PDLA) and poly-D, LLA (PDLLA) (Griffith 2000).

Properties of PLA

It is a versatile biodegradable polyester. PLA can be crystallized into 3 forms α, β,γ (Lim et al. 2008). Production of PLA from LA is of great demand, because of the various properties of PLA. It is a semi-crystalline polymer having melting point of 170-180°C. Different physical characteristics (heat capacity, density, mechanical and rheological properties) rely on its transition temperatures (Henton et al. 2005). It has glass transition temperature of 60-65°C (Tg). PLA is not water soluble, but soluble in chlorinated solvents, benzene (hot), tetrahydrofuran and dioxane.

Uses of PLA

PLA can be processed via extrusion, injection molding, thermoforming, fibre spinning etc to form various useful products. In market it is generally available as thin films, plastic pellets, or 3D printable filaments. It is used for food packaging because of better printability, resistance to grease and oils, and decreased issues related to taste and odour transfer. PLA can be transformed into thin fibres, which are used for the manufacture of sports apparel, upholstery material, hygiene products, diapers etc.

Implants

PLA is widely used in biomedical field because it can be degraded into non-toxic lactic acid. Various medical implants such as screws, wires, pins, rods, meshes etc are made using PLA. These implants break down inside the patient's body within one year thereby eliminating the requirement of any further surgery. PLA is also used in facial surgeries.

Tissue Engineering

Because of its biodegradable property, PLA is also used in tissue engineering. The mechanical properties of PLA were everaland copolymerization. Due to their compatibility PLA can blend with other polymers producing porous scaffolds by various techniques such as electrospinning, particle leaching and foaming. Zhang et al. 2011 invented PLA/octadecyclamine functionalized nanodiamond (ND-ODA) composites to use in tissue engineering purpose.

Drug Delivery System

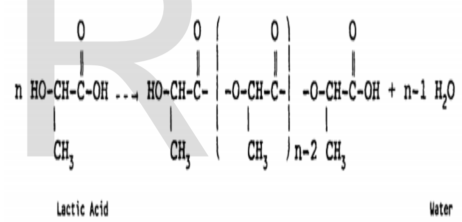
PLA can be used for the production of dosage forms like pellets, microcapsules, microparticles (MP), nanoparticles (NP). The MP and NP of PLA both in modified and unmodified forms are being used in RNA/DNA drug delivery applications due to their small size which helps them become permeable through biological barriers like blood-brain barrier (Roney et al. 2005).

Synthesis of Poly Lactic Acid (PLA)

Poly lactic acid is highly versatile, biodegradabale, aliphatic, potential polyester that can be produced from 100% renewable raw materials (Auras et al. 2010). The synthesis of PLA starts with producing LA first, followed by polymerization of LA by several methods.

i. Direct Condensation Polymerization

Usually it produces low molecular weight polymers, which are later converted to high molecular weight polymers by adding chain coupling agents. Polycondensation of lactic acid is a comparatively simple process to produce PLA. In presence of hydroxyl and carboxyl groups, LA monomers can undergo self- esterification, leading to reversible polymerization and produce water as a by-product. To remove water from the solution, high temperature and vacuum are used.



Earlier it was believed that, polycondensation process cannot produce high molecular weight polymers, because of LA having difficulty in driving the equilibrium to esterification, which is necessary to obtain high molecular weight PLA. This problem was solved by using ether as an organic solvent (eg: diphenyl ether).

ii. Melt Polycondesation

Usage of organic solvents requires complex processes that makes it expensive, also it becomes difficult to remove the solvent completely from the final product. To avoid this problem, and to produce high molecular weight PLA at a low cost, melt polycondensation process was developed. This process was first reported by Kimura and co-workers. Aqueous L-lactic acid(LLA) solution is dehydrated and oligomerized to obtain LLA oligomers; and then it produces PLA pre polymers by melt polycondensation. It is then crystallized by solid state polycondensation below melting temperature to achieve high molecular weight PLA (60,000Da). This process takes relatively lesser time.

iii. Ring Opening Polymerization (ROP)

It is the most common process for the production of high molecular weight PLA (Auras et al. 2010). It involves opening of ring of the lactic acid dimer with the help of a catalyst. The process consists of three steps: polycondensation, depolymerisation and ROP. This route requires additional

purification steps, which are relatively complicated and expensive. ROP of the lactide needs a catalyst, but it results in PLA with a high molecular weight. It is possible to control the ratio and sequence of D- and L-LA units in the final polymer by controlling residence time and temperatures in combination with catalyst type and concentration (Gupta et al. 2007). It is catalysed by transition metals such as tin, aluminium, lead, zinc, bismuth, ion and yttrium (Agrawal and Bhalla 2003). Azeotropic dehydration is a direct method for synthesis of high molecular weight PLA (Garlotta 2001).

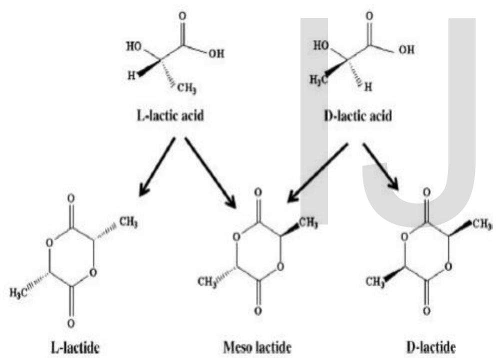


Fig5: Different Stereoforms of Lactide

iv. Microwave Irradiation

Microwave irradiation is a well-known method for drying and heating materials and is widely utilized in industry as well as in home kitchen for those purposes. Furthermore, microwave heating has been used by many researchers in chemical synthesis because of its high efficiency, speed and uniform heating. Almost every modern organic and pharmaceutical chemical laboratory is equipped with some kind of microwave synthesizer due to greater reaction speeds attributed to it. These enhanced reaction rates are usually explained by the greater reaction temperatures that are achieved by faster and more thorough heating induced by microwaves and usage of closed and usually pressurized reaction vessels or reactors. The closed reaction vessels allowed replacing high-boiling solvents with, easier to deal with, low-boiling solvents, further simplifying isolation and purification of products. Furthermore, the direct heating of molecules under irradiation by microwaves leads to very fast and homogenous heating, resulting in diminished side reactions, higher yields and cleaner final products.

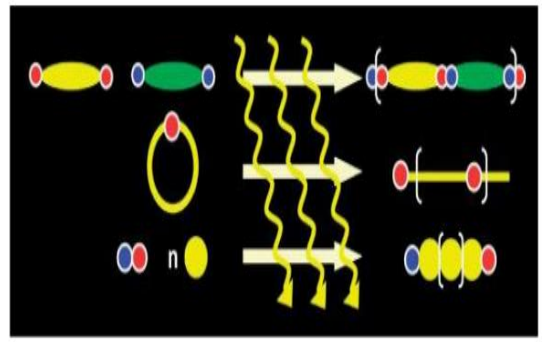


Fig6: Simplified scheme of possible Microwave-assisted polymerization reactions

Originally microwave energy was applied for heating of food products by Percy Spencer in the 1940s. Since the 1950s, microwaves found multiple application possibilities in chemical and related industries, in particular: food industry, drying and polymer industries. Other possible applications include analytical chemistry, biochemistry and even for specific medical treatments. Recent availability of modern microwave reactors, which provided online monitoring of temperature and pressure in sealed off vessels with standard solvents, succeeded in bringing back popularity to this method.

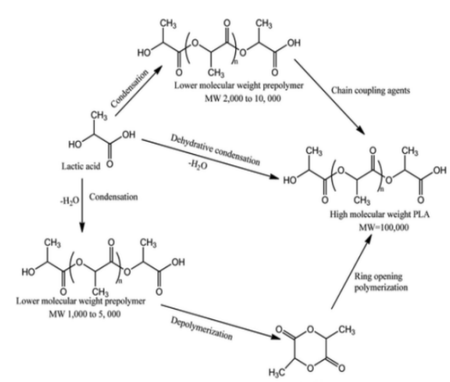


Fig7: Schematic Representation of PLA Synthesis Methods

Conclusion

Direct Condensation Polymerization

Disadvantages of this route are the requirement of relatively large reactors and huge energy consumptions for necessary high temperature and vacuum leading to expensive final product. Furthermore, LA is known to undergo racemization at high temperatures thus the final product could be lower than expected quality.

Melt Polycondesation

A lot of efforts were put into industrializing this process, but it was not successful due to relatively slow reaction rate thus leading to very long reaction times needed to achieve high molecular weight and, at least for now, deeming this process economically ineffective.

Ring Opening Polymerization (ROP)

Due to its efficiency and low toxicity, making it one of the best choices to use for production of biodegradable and environment-friendly polymers like PLA.

Currently, the biggest producer of PLA, Nature Works (NB, USA) produces PLA with L-Lactic acid content of 94% using specific solvent free process where combination of melt polycondensation and ROP is utilized. Furthermore, ROP currently dominates as the process of choice for industrial PLA production due to low time consumption and a high molecular weight final product, making it probably the most used and viable method to produce PLA, although high temperatures and low pressure must be still used to achieve the final product.

Microwave Irradiation

It still shows that microwaves are potentially fast and efficient way to synthesize smaller amounts of polymer thus it could be considered as great option for laboratory experiments or small scale needs. However, as the microwave radiation has a very short permeation into the sample, it is difficult to design an industrial process which could be effective enough to produce economically sufficient amounts of PLA. As the technology is advancing and new reactors are created, microwave irradiation could become a great alternative for standard heating, as faster and less energy consuming method to obtain PLA.

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