



HAL
open science

Review: Syntheses of poly(lactic acid)s and their block copolymers for Drug Delivery Applications

Linda W Oktavia, Didier Bégué, Patricia Targon Campana, Roger Hiorns

► To cite this version:

Linda W Oktavia, Didier Bégué, Patricia Targon Campana, Roger Hiorns. Review: Syntheses of poly(lactic acid)s and their block copolymers for Drug Delivery Applications. *Polymer international*, 2023, visionary polymer research for a better world, 72 (10), pp.881-898. 10.1002/pi.6529 . hal-04265197

HAL Id: hal-04265197

<https://hal.science/hal-04265197v1>

Submitted on 30 Oct 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Review: Syntheses of poly(lactic acid)s and their block copolymers for Drug Delivery Applications

Linda W. Oktavia,¹ Didier Bégué,¹ Patricia Targon Campana,^{*2} Roger C. Hiorns^{*1}

¹CNRS/Univ Pau & Pays Adour, Institut des Science Analytiques et Physico-Chimie pour l'Environnement et les Matériaux, UMR5254, 64000, Pau, France.

²School of Arts, Sciences and Humanities, University of São Paulo, 03828000, São Paulo, SP, Brazil.

Communicating authors: pcampana@usp.br ; roger.hiorns@univ-pau.fr

ORCID: Patricia TARGON CAMPANA is <https://orcid.org/0000-0002-2337-6372>

ORCID: Didier Bégué is: <https://orcid.org/0000-0002-4553-0166>

ORCID: Roger C Hiorns is: <https://orcid.org/0000-0002-9887-5280>

Abstract

Since the advent of supporting matrices for biological applications, many types of drugs have been administered *via* various forms of conventional drug delivery preparations, such as pills, solutions, creams, suppositories, injected gels, and so on. Key parameters to all these systems for effective drug delivery are controlled release for sustained periods, targeted delivery, and enhancements of drug stability and efficacy, all of which can be manipulated by using polymers. Given the important impact of the structures of the polymers on these parameters, this mini-review gives a simple introduction to the requirements of drug delivery systems and surveys the synthetic pathways to a key polymer in this field, namely poly(lactic acid) (PLA). We also review the preparation of block copolymers that incorporate PLA, to expand and further develop its properties for drug delivery systems. It is hoped that this short teacherly and introductory review will provide a basic stepping-stone to more in-depth reviews and papers, and enable an easy access to this fast growing field.

1. Introduction

Polymers and their composites are widely used in drug delivery systems to carry a range of molecules such as peptides, proteins, genes and small drugs.¹ Their syntheses are wide ranging, and have a massive impact upon their drug delivery properties. This paper gives a short teacherly review which introduces the various routes used to make one of the key polymers in drug delivery systems, poly(lactic acid) (PLA). The syntheses of PLA are also comparable to many polyesters, such as poly[lactic-*co*-(glycolic acid)]s (PLGAs), and poly(ϵ -caprolactone)s, mainly coming from polycondensations or ring opening polymerizations (ROP). We also give a brief mention to poly(ethylene oxide) (PEO), often commonly called poly(ethylene glycol) (PEG), which like PLA occupies an exceptionally important role as a drug delivery agent, for example in the recent vaccines widely used against COVID. We then go on to briefly consider key developments in the syntheses of block copolymers from these materials, and finally touch on modelling, an important subject which is starting now to reduce the requirement to prepare large libraries of materials by predictively selecting target materials of interest for their physical qualities such as melting points, optical properties and macromolecular self-assembly. It is hoped that this work will provide a stepping-stone to other more in-depth reviews and papers in the field.

2. Drug delivery systems

We start first with a consideration of drug delivery systems, and the constraints that are placed on polymers. The history of drug delivery began in the mid 1800's with Lafargue who developed the first known controlled delivery system. It released morphine directly to the affected area via lancets. This method fell into disuse due to the adoption of intravenous injections. After 150 years, the interest in controlled release systems reemerged and since then, many types of drugs have been given through various preparations such as simple solutions, lotions, creams, pastes, ointments, powders, suppositories, suspensions, and injections,² to more complex systems such as films, capsules, subdermal implants, and patches for sustained release.

Indeed, during the past half-century, drug delivery matrices have evolved from bioinert to bioactive materials, that is to say from biocompatible materials with minimal immunological response into materials that actively participate in the healing process. These bioactive materials can act in a specific manner on recovering organs or tissues at the level of cellular stimulation.³ In addition to controlled morphological and mechanical characteristics, new drug delivery systems have been developed for controlled multiple and sequential activities. For

example, the same material is able to release growth factors, vitamins, nucleic acids, and factors for cell differentiation while simultaneously serving as a physical support for cell growth and tissue repair. To accomplish these activities, there are key properties that require careful consideration. They include: the relative solubility of the material to enable the binding and the releasing of biomolecules; a moderate robustness to keep the drug stable to its final destination; and a reduced toxicity to minimize inflammatory reactions from the immune system. In this sense, research is aiming for systems that can enable stable, controlled, and sustained delivery to well-targeted sites in the body.

Thus, the overarching aims of effective drug administration are to increase the pharmacokinetics and pharmacodynamics of each therapy to enable the administration of drugs to the right place, over a determined period of time with controlled, focused concentrations.

The key points of focus for drug delivery systems can then be more generally considered as:

Controlled and sustained release

The efficacy of the drug can be increased by maintaining a concentration that is within the effective dose range. The loaded polymer carrier allows controlled temporal and spatial release of the drug by controlling drug diffusion, dissolution rate, or carrier degradation.

Stability enhancement

Low drug stability often reduces the effectiveness of promising therapy candidates, either because the drug is removed by the body or reacts in an untargeted manner before reaching its destination. This is particularly true when using hydrophobic drugs which require hydrophilic encapsulation.

Targeted delivery

Drug targeting makes it possible minimize drug dosages by guiding it to the specific site where its action is required. This reduces undesirable side effects. Targeting can be achieved by coating or conjugating carriers with affinity reagents such as nucleic acids,⁴ proteins,⁵ peptides⁶ and antibodies.⁷

Polymers and copolymers have been widely used in drug delivery systems, mainly due to their physical and chemical properties, which can result in timely, environment specific degradation, in addition to their controllable preparation and versatility. Their use has resulted in the development of composite systems with bioactive molecules with increasing biological interactions, stimuli of specific cellular responses, and directing cell proliferation and differentiation.²

Furthermore, polymers can be assembled into a range of structures at two different levels: two-dimensional thin films and micro- and nanoparticles or nanotubes; and three-dimensional porous and nano- and micro-fibrous scaffolds. This level of control over several scales means that a range of materials can be envisaged to support specific, desired properties in drug delivery systems, as shown in Table 1.

Class of drug delivery system and types of polymers used	Advantages	Limitations
<i>Microparticles</i>		
<ul style="list-style-type: none"> • biodegradable polymers (poly(lactic acid), poly[(lactic acid)-co-(glycolic acid)], polyanhydrides, etc.) • natural polymers 	<ul style="list-style-type: none"> • protection of drugs from the environment • sustained release is achievable 	<ul style="list-style-type: none"> • low reproducibility
<i>Nanoparticles</i>		
<ul style="list-style-type: none"> • biodegradable polymers • natural polymers 	<ul style="list-style-type: none"> • stable delivery system • precisely controlled release rates and/or targeting to specific body sites 	<ul style="list-style-type: none"> • difficult to scale-up
<i>Micelles</i>		
<ul style="list-style-type: none"> • amphiphilic block copolymers 	<ul style="list-style-type: none"> • increasing solubility of highly lipophilic drugs • enhanced solubility for hydrophobic drugs 	<ul style="list-style-type: none"> • low stability; may require additional crosslinking
<i>Drug conjugates</i>		
<ul style="list-style-type: none"> • hydrophilic polymers • dendrimers 	<ul style="list-style-type: none"> • extended circulation half- life, reduced clearance due to increased drug hydrodynamic radius • drug release in a controlled manner 	<ul style="list-style-type: none"> • low drug-loading capacity • activity of drug can decrease due to conjugation • approach provides sustained but not controlled release
<i>Scaffolds including those based on nano and micro-fibres</i>		
<ul style="list-style-type: none"> • hydrophilic polymers (hydrogels) • biodegradable polymers (e.g. PCL, PLA, PLGA etc.) • natural polymers (fibrin, chitosan, and collagen) 	<ul style="list-style-type: none"> • tunable chemical and physical properties • permits various routes to drug incorporation <i>via</i> encapsulation into the fibres for homogeneous drug distribution or surface binding • improved patient compliance due to infrequent dosing 	<ul style="list-style-type: none"> • release may be restrained by chemical binding • drug compatibility with the polymer may limit utility • delivery may require incision or large-gauge needles • risk of localized dose-dumping, i.e., inhomogeneous drug distribution

Table 1. Notable advantages and limitations of polymer-based drug delivery systems.

The applicability of the different structural classes presented in Table 1 is related to the route of administration. In controlled and sustained drug systems development, the parenteral and oral routes have received by far the most attention, but in recent decades, the transdermal

route has been gaining more attention. Table 2 shows some of the main routes and the delivery system used.⁸

<i>Route</i>	<i>Physiology</i>	<i>Delivery system</i>
parenteral	administered outside of the gastrointestinal tract (GI) with injectables such as intravenous or intraarterial, subcutaneous, intramuscular	<i>intravenous or intra-arterial</i> : suspensions, sparingly soluble derivatives and biodegradable microspheres. <i>intramuscular and subcutaneous</i> : absorption from aqueous solutions and suspensions, oil solutions
oral	drug absorption and transit via the GI tract	pellets and tables are used to target a sustained release, and control is attained by monitored oral administration
buccal and sublingual	drug absorption from the oral cavity through the oral mucosa (sublingually or between the cheek and gingiva)	saliva-activated adhesive systems: films
transdermal	avoiding the GI tract, provides controlled administration, reducing side effects and inadequate dosing; it enhances the therapeutic efficiency	patches: polymeric scaffolds and films.
implantable	targets action of the drug, but may require surgery to implant and remove	biodegradable polymeric implants: 3D scaffolds; drug conjugates.

Table 2. Main routes for drug administration.

Polymers are now important for all of the described routes, their properties being allied closely to the needs of these applications. A particular exemplar is that of transdermal patches, which can be improved by using amphiphilic polymers as the supporting scaffold, to adsorb and then de-adsorb the medication in a controlled and localized way.^{1,9}

Each delivery system presented in Table 2 is more appropriate to one route or another in accordance with the physiology met by the drug.¹⁰ Interestingly, one can also consider three types of release mechanisms: pump-controlled; diffusion-controlled; and chemically controlled. The last two are heavily impacted on by the polymer structure, not only by factors such as amorphous qualities allowing easier drug releases, but also by macromolecules having programmed degradations to enhance these qualities.

3 Poly(lactic acid) and poly(lactide) (PLA)

Poly(lactic acid), also called poly(lactide) (PLA), is a bio-based polymer used in a variety of applications due to its high strength modulus, bio-compatibility, biodegradability, and the non-toxic nature of its degradation products through hydrolysis.¹¹ These properties have meant it has found wide usage, both for drug delivery but also formed as implants, either alone¹² or in blends and composites.^{13,14} Its industrial life-cycle has been excellently reviewed,¹⁵ and it is very much touted as a material for wider use given that its monomers are biosourced from the fermentation of organic materials.¹⁶ Very recently, a short series of papers edited by Brzeziński and Basko details the way in which its properties can be varied, with a range of mechanical and chemical means.¹⁷ As discussed in more detail below, it can be made from lactic acid or from lactides, thus explaining how the same polymer has two names.

PLA is a thermoplastic aliphatic polyester. It originates from naturally occurring organic acids i.e., lactic acid, which is derived from carbohydrates.¹⁸ PLA can also be recycled back into its monomer by hydrolysis or thermal depolymerization. The polymer has many excellent properties which are demonstrated by its processing: it can be used in extrusion molding, injection molding, and can be spun or drop cast. In general, PLAs show high mechanical strengths and moduli. Table 3 lists some of the properties of PLAs. These can vary quite significantly with the stereo-structure of the polymer and its molecular weight.

Not only is PLA bioderived, it is also biocompatible and can be used as a drug delivery support with various therapeutic agents, such as simvastatin for bone regeneration¹⁹ chemotherapy drugs^{20,21} and antibiotics.^{22,23} Interestingly, PLA is completely absorbed by the body and the rate of this depends on the molar mass and the stereo-structure of the polymer chains.²⁴

PLA's mechanical performance and physical properties, combined with its high degree of bio-compatibility, means that it is particularly well-placed for use in a wide variety of drug delivery systems, for example as PLA nanofibers loaded with the chemotherapeutic molecule paclitaxel and C₇₀ water-soluble fullerenes,²⁵ PLA/poly(ethylene oxide) electrospun fibers for protein delivery²⁶ and PLA 3D porous scaffolds for sustained protein release controlled by pH.²⁷

glass transition temperature, (T_g)	50-64 °C
melting temperature (T_m)	145-186 °C
tensile strength	28-50 MPa
Young's modulus	1.2-3 GPa
elongation at break	2-6%

Table 3. Key physical properties of PLA homopolymers.²⁸

3.1 Syntheses of poly(lactic acid)s and poly(lactide)s and their monomers

There are two main options with respect to the synthesis of PLA, namely: direct polycondensation of lactic acid; and ring opening polymerization (ROP) of lactides using a suitable catalyst.²⁹ It should be stated that so-called green processes, that is techniques that do not use metals with often not well understood toxicities, are continuously being developed. Historically, a major milestone from an industrial viewpoint is Cargill Inc.'s development of high molecular weight poly(L-lactic acid) (PLLA) by ROP at large scales.³⁰

The method of direct polycondensation requires particular conditions to obtain high molecular weight polymers, namely 180-200 °C, long reaction times that might be several days, and a way of removing the condensed water to drag the reaction forward, for example by using a reduced pressure. Compared to this, ROP is capable of producing high molecular weight PLAs with low dispersities ($D = M_w/M_n$) in short times, that might be a matter of minutes or hours and under relatively mild reaction conditions, i.e., around 110 °C,³¹ or slightly higher when pushing for complete consumption of the monomer.³² As a result, the ROP of lactides has been widely adopted for the production of PLA.

Lactic acid (2-hydroxypropanoic acid), with its chiral carbon, exists as two optically active stereoisomers, with L and D indicating their absolute configurations. It should be noted that these terms, while widely used, are not recommended by IUPAC, and the preferred, respective terms are the stereodescriptors *S* and *R* for the isomers.³³ Figure 1 shows the structures.



Figure 1. Structures of: (a) (*R*)-lactic acid, often termed D-lactic acid; (b) (*S*)-lactic acid, widely called L-lactic acid; and (c) a racemic mixture of (*S*)-lactic acid and (*R*)-lactic acid, called (*RS*)-lactic acid or *rac*-lactic acid.

The lactide molecule, however, has two stereocenters, and thus there are three types on monomer, as shown in Figure 2. There is also a term for the 1:1 mixture of two racemate molecules, *rac*-lactide.

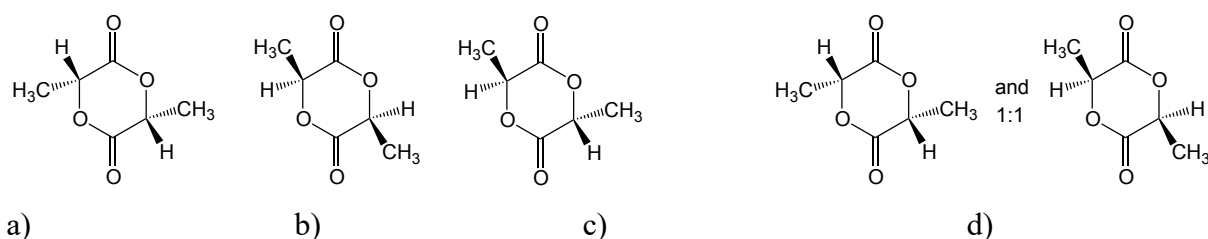


Figure 2. Structure of the various lactides from left to right: (a) (*R,R*)-lactide, previously often called D-lactide; (b) (*S,S*)-lactide, commonly called L-lactide; (c) (*R,S*)-lactide, often called *meso*-lactide; and (d) a mixture of (*R,R*)-lactide and (*S,S*)-lactide, called *rac*-lactide, following recent changes in IUPAC nomenclature.³³

Figure 3 shows the overall method used to make lactides. The first step is to make the oligo(lactic acid) (OLLA) from a lactic acid. The stereochemistry is retained, mostly, during this process. An unzipping reaction, as shown in Figure 4 is then performed, often in highly alkaline conditions. Organotin compounds are used also, however, work has found that higher yields can be obtained when using thermal processes in the presence of small organic additives.^{34,35} More recently, zeolites have been found effective in promoting pyrolysis of PLA to yield the lactide, however, thermal mechanisms are understood to be *via* numerous competing routes.³⁶

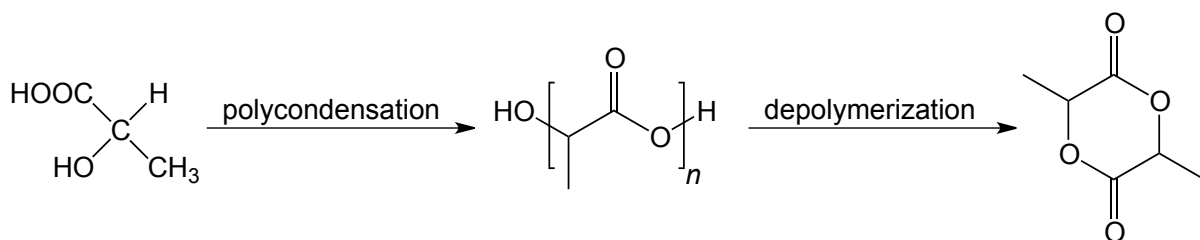


Figure 3. Preparation of lactide from lactic acid *via* the formation of an oligolactide (OLLA). The crude lactide requires purification by crystallization from solution or melt prior to use. Adapted from reference 30.

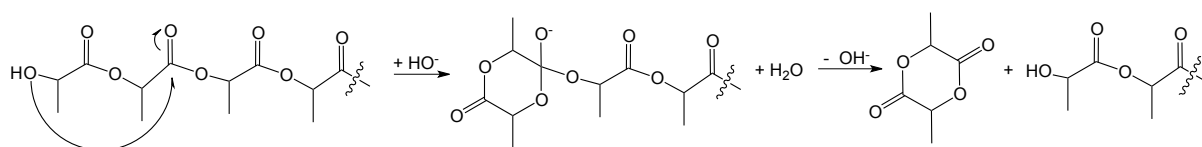


Figure 4. The traditional, summary mechanism for the degradation of PLLA in alkaline media to yield lactides, adapted from references 36 and 37.

Figure 5 summarizes the two main synthetic routes to PLA, either lactic acid polycondensation or a ROP of lactide. Its history and synthesis are well reviewed by Masutani and Kimura,³⁰ and a more general short review places its syntheses within a green perspective.¹⁶ The polymerization of pure (*R,R*)-lactide (D-lactide) and (*S,S*)-lactide (L-lactide) produces isotactic, crystalline polymers that are commonly and respectively called PDLA and PLLA. Another excellent review of both these processes is given by Pretula *et al.*²⁹

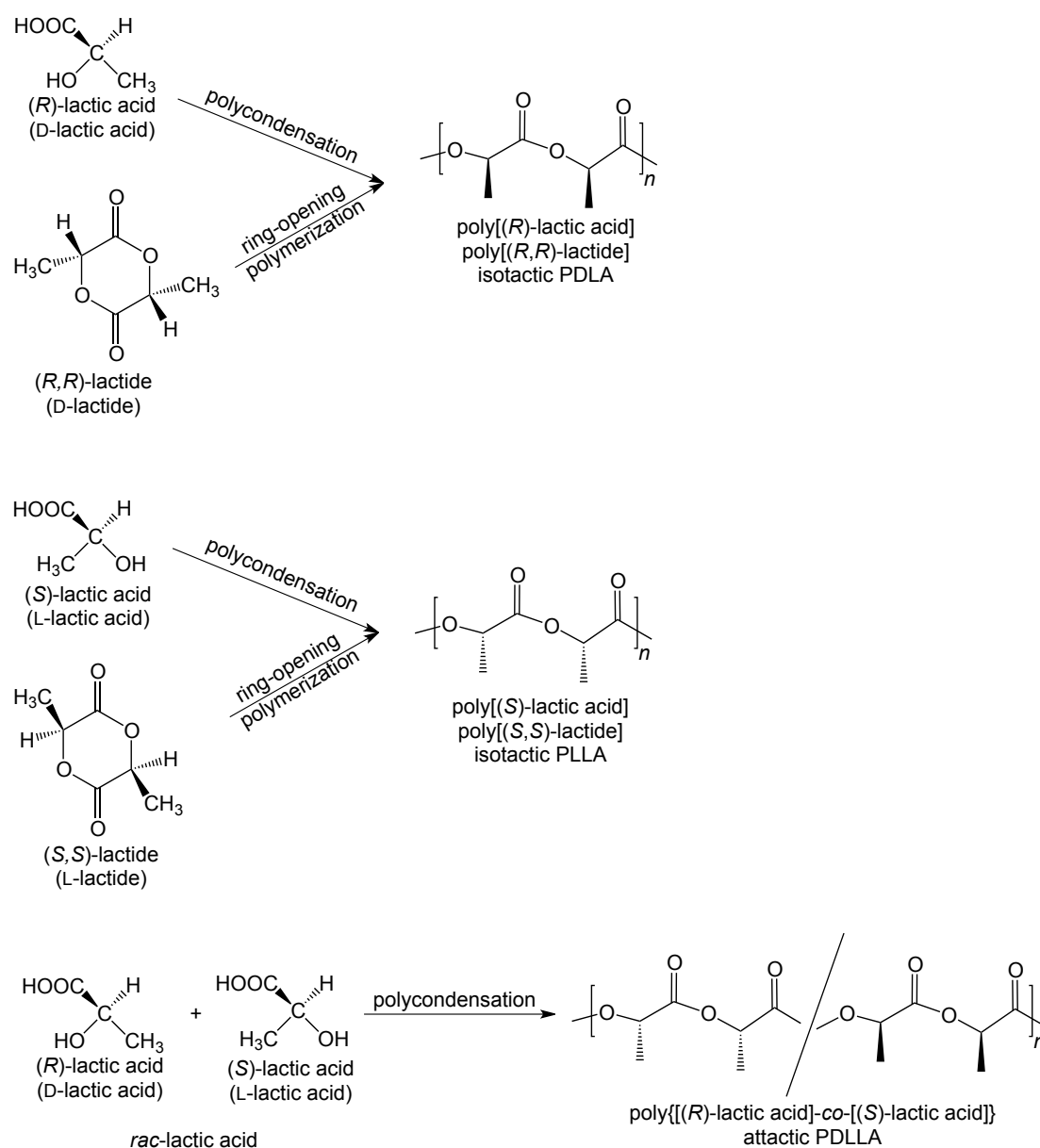


Figure 5. Syntheses of PLA *via* various routes to give isotactic and atactic polymers. Note: here we provide both the IUPAC names above and some older names below which can still be often encountered. Adapted from reference 30.

3.1.1 Polycondensations of lactic acid

PLA with very high molecular weights, i.e., above 100 kg mol^{-1} , can be prepared by the so-called direct polycondensation of lactic acid (i.e., without going *via* a prepolymer or lactide formation). As we mentioned above, overcoming the removal of water, and keeping it below 1 ppm during the reaction, is essential when aiming for high molecular weights.^{30,38}

The polycondensation can be performed in solvents or at high temperatures in the bulk. In solution, a solvent is simultaneously used to remove water by boiling it off, and the reaction is thus promoted by the use of a solvent that forms an azeotropic with water.¹⁶ In the bulk, high

temperatures, typically greater than 150 °C, are used to drive the reaction forward in an initial step to form the prepolymer (low molar mass products often around several thousand g mol⁻¹).³⁹ These can then be dried, and the reaction further pushed forward. At this point, the reactions between prepolymer chain-ends are essentially at the surfaces of contacting crystals, and because of this the control over the temperature is extremely important to reach high molecular weights, with optimal values around 140 °C in the presence of an acid catalyst such as dodecylbenzenesulfonic acid.⁴⁰ Again, very high molecular weights can be obtained by when using a catalyst (tin 2-ethylhexanoate, i.e., Sn(Oct)₂) combined with an organic acid such as *p*-toluene sulfonic acid. Extremely high molecular weights, above 500 kg mol⁻¹, are accessible.^{29,41,42} The bulk reactions are particularly well reviewed in reference 43.

Even though Sn(II) is approved by the FDA for use at very low concentrations, typically 10 ppm for lactic acid polymerizations,²⁹ it should be noted that there is particular concern as materials are often used for drug delivery or insertion into the human body. While the toxicity of the compound is reduced as the alkyl chains increase in length, organotin compounds are known to disturb signaling pathways, cause apoptosis, and inhibit T-cell immune responses and enzymic actions.⁴⁴ There is considerable discussion around this subject area as the actual critical level of tin concentration is not clear, as it varies greatly with each compound and can impact in different ways. Even food poisoning, for example by excessive and poor use of tin cans,⁴⁵ remains unclear. However, what is absolutely clear is that dialkyltin compounds do severely impact on immune systems and act as potent neurotoxicants, even at extremely low concentrations,⁴⁶ leading to behavioral degradation⁴⁷ and therefore the exclusion of tin is thus a worthy route to follow. Work in this direction is advanced, for example with metal oxides, however, as yet most of the products are either colored or with low molecular weight. Particular interest can be given to work using microwaves to speed the reaction⁴⁸ or the use of organic acids.⁴⁹ There is more scope though for the use of organic catalysts in ring opening polymerizations, as we find below.

3.1.2 *Ring-opening polymerizations (ROP) of lactides*

Lactide polymerizations have been performed using several routes, including coordination polymerization with organometallic compounds, cationic polymerizations with strong acids, and anionic polymerizations. In the latter, there are two subgroups: polymerizations initiated by an anion or by an anion resulting from activation through OH group transfer, at the initiation stage. This has been under active development and uses organic, non-metallic catalysts and/or initiators. Only a few systems provide “living” controlled polymerizations. In order to attain

very high molecular weights, *i.e.*, with molecular weights around 10^6 g mol⁻¹, reactions usually involve Sn(II) or Zn, however, for most drug delivery applications, lower molecular weights are more than ample, and this leaves open a wide door for the use of organic catalysts.

Many studies have been carried out studying the polymerization of lactides with various metals and rare earth complexes as catalysts for the ROP of lactides.⁵⁰ Typically dialkylalkoxy or (multi) alkoxy ligands are used with metals to give structures such as R₂ROM, or (RO)₃M. This said, by far the most commonly used catalyst is Sn(Oct)₂ with the initiator 1-dodecanol. It has delivered consistent high molecular weights, high activities at low concentrations, and importantly for applications outside of drug delivery such as packaging, PLAs without color tints. Extremely recent work, published in this same series,⁵¹ shows that liquid Sn(OnBu)₂ is more efficient than the commonly reported Sn(Oct)₂ system, lending the possibility of reducing further tin concentrations.

The generally accepted mechanism is that based on a coordinated insertion.^{52,53} Detailed modelling has reinforced this view, and indicated that the reaction follows a reversible chain transfer which leads to relatively low dispersities.⁵⁴ These values can even reach around 1.1, although more commonly are above 1.2 but well below 2. More recent work has found that methanol is one of the most effective alcohols to use as it leads to the highest molecular weights and defect-free structures.⁵⁵ As shown in Figure 6, in the first step, the alcohol initiator reacts with the metal alkoxide to undergo a ligand exchange, and creates a metal alkoxy group that is coordinated with the carboxylic lactide. The resulting intermediate structure is unstable, and leads to a breakage of the lactide ring. The reaction propagates by the continued insertion of lactides at the tin-oxygen bond. In effect, this type of polymerization is *pseudo*-living, and the molar mass can be controlled relatively well. However, in the last latter stages of propagation, when the monomer concentration is low, reverse depolymerization by back-biting can occur. As each chain carries an ester group at the end, *trans*-esterification between chains can also happen, again broadening the molar mass distribution. The presence of residual metals can promote the subsequent degradation of the polymer, acting as catalysts to reduce the temperature at which degradation occurs.⁵⁶ Thus phosphites are added to stabilize the material and improve processing.^{57,58}

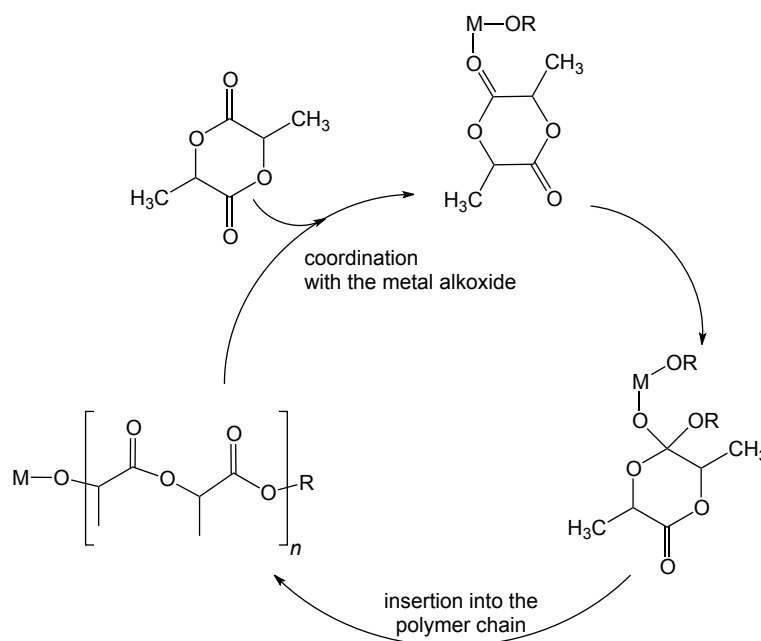


Figure 6. Steps in the ROP of lactides with tin octoate, adapted from reference 59.

Acting in a similar manner to tin-based catalysts, zinc is finding increasing favour given its complete non-toxicity. Indeed, it has been shown to be of use in the ROP of both LA and ϵ -caprolactone in the same reactor with the systems in Figure 7.⁶⁰ Excellent stereoselectivity has been shown, and molecular weights (M_w), consistently in the high tens of thousands, but also reaching above 10^5 g mol^{-1} .

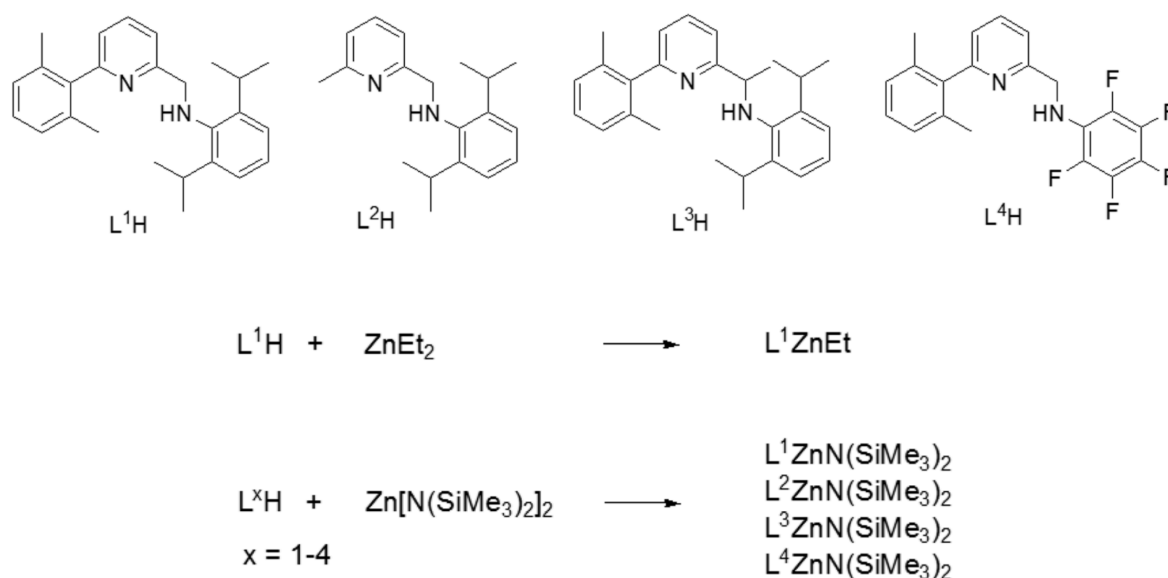


Figure 7. Ligands developed for ROP of LA and ϵ -caprolactone using Zn in place of Sn.⁶⁰ Reproduced with permission from the RSC.

Cationic catalysts, such as acids, and typically quite strong acids such as trifluoromethanesulfonic acid, can be used to perform ROPs of lactides. The initiation proceeds by the protonation of the monomer by the acid, as shown in Figure 8. This new molecule then reacts with the alcohol-based initiator. The subsequent loss of the acid results in a ring opening and the production of a chain with an alcohol at the chain-end. This new alcohol can then react again with a protonated monomer and the cycle results in the preparation of a chain. Beneficially, the acid catalyst is easily removed from the mixture, and this is a clear advantage over alkoxide metals which remain attached to the chain at the end of the reaction. Similarly, the polymerization retains good stereospecificity. A downside of this polymerization is, however, the presence of chain terminations and chain transfer reactions. Also, it tends to have a low polymerization rate, leading to relatively low molecular weights.

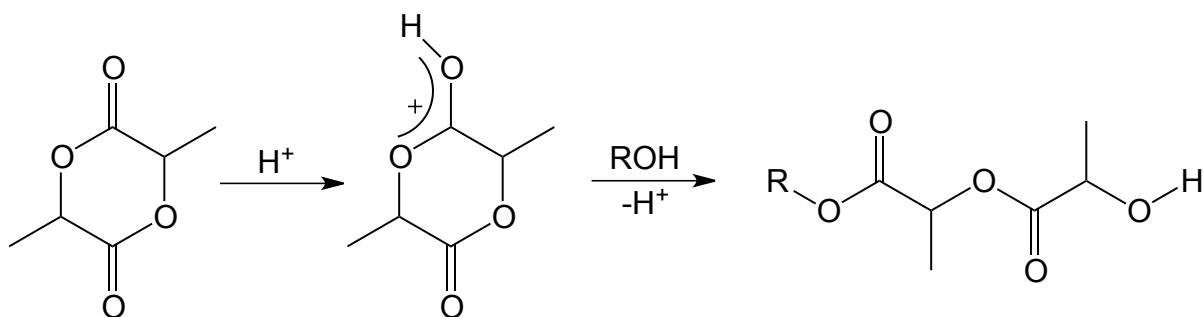


Figure 8. The overall reaction creating PLA from a lactide. Adapted from reference 61.

The study of the anionic polymerization of lactides began in the mid-1990s. The first works used zwitterions based on amines and phosphines. To date, most of the (super) strong bases have been used to initiate the polymerization of LA and ϵ -caprolactone. For the initiation with zwitterions (Figure 9) alkoxide anions are formed and used as the active centers. For example, phosphazenes can convert alcohols into alkoxide anions with large cationic counterions.^{62,63} Generally speaking though, 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) is more popular than phosphazene. The use of a large cationic counter ion can reduce the degree of aggregation during the polymerization.



Figure 9. The generation of a zwitterion for the subsequent anionic polymerization of lactides.

Another, alternative process involves the formation of highly active species, as a result of hydrogen bonding, and is presented in Figure 10. In these highly active systems, it is not completely clear as to what degree the reaction proceeds through the formation of oxyanions or -OH groups activated by H-bonding.^{64,65} Interestingly, this system does give a substantial number of large macrocycles. This is an exciting new field of ROP research, as it can provide PLA macromolecules that are more stable than linear ones because depolymerization usually occurs at the chain-ends. Baško's research has observed this internal stabilization for LA cationic polymerization.⁶⁵ With some other organocatalysts, it is assumed, that the simultaneous activation of LA and alcohol (used as an initiator) occurs.⁶⁶

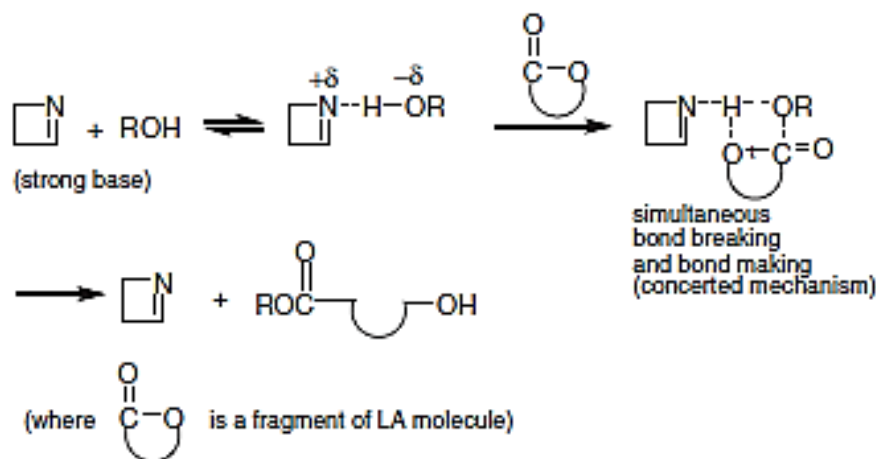


Figure 10. Formation of anions to initiate anionic polymerizations, reproduced with permission from Elsevier.²⁹

A special mention must be given to carbene chemistry. Carbenes are very useful in that the singlet carbene can, by back attack on the ester carbonyl carbon thus activate the monomer and lead to a ROP of an ester. The first examples of their use were back in 2002.⁶⁷ An excellent review appeared back in 2013 by Taton and colleagues of the general applicability of carbenes

to polymerizations,⁶⁸ and a more recent review has also appeared which clearly addresses the problems confronted when developing organic catalysts for the ROP of LA.⁶⁹ This said, interesting work, on several levels, has also made possible the continuous production of PLA with carbene-based catalysts. In this work by Mincheva *et al.*⁷⁰ the ROP with carbene is optimised and then used in continuous production with an extruder in a solvent-free bulk polymerisation. An additional benefit was that the *N*-heterocyclic carbene (NHC) was stable enough to prepare under air and could easily be coupled with Mg. In the optimised result, molecular weights (M_w) of several tens of thousands were achieved, although the relatively high temperatures, around 200 °C, are costly. Figure 11 shows their proposed mechanism.

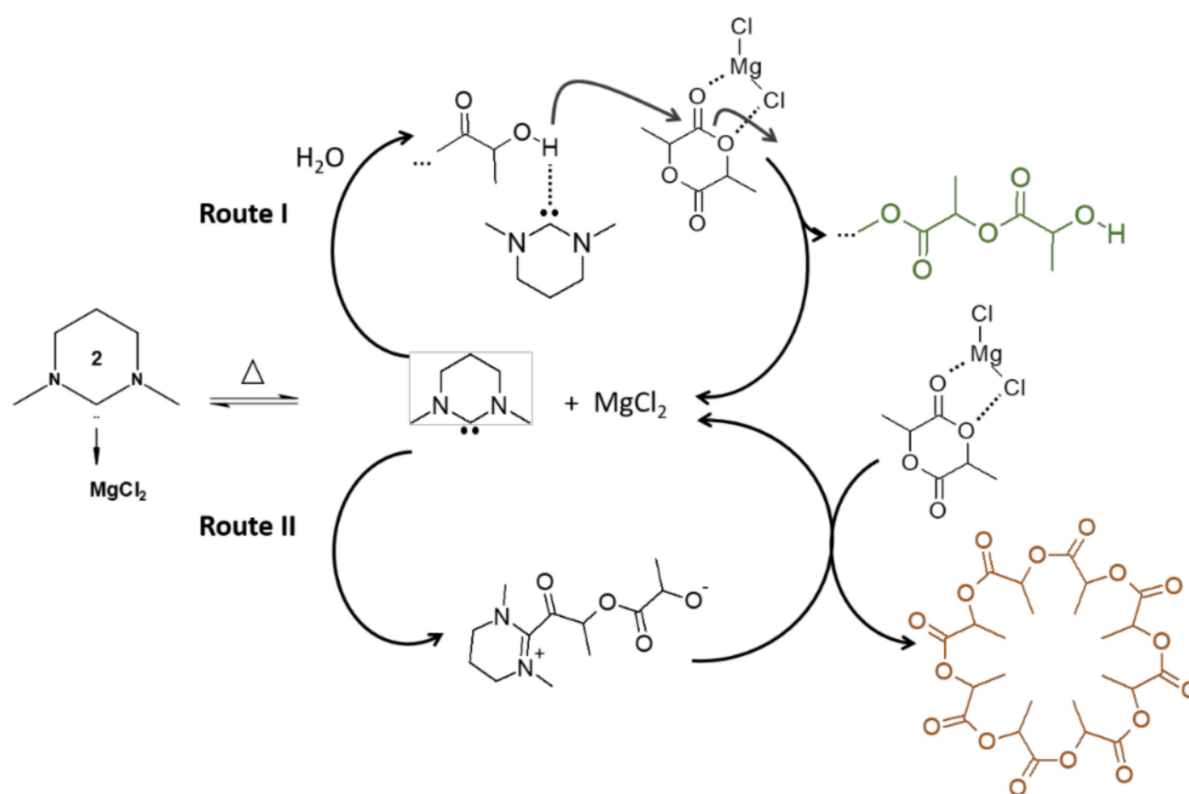


Figure 11 Proposed mechanism for NHC polymerisation of LA with Mg, reproduced from reference 70 by courtesy of MDPI.

An alternative method includes the use of carbene complexed with iron by Nylund *et al.*,⁷¹ where incidentally they also give a clear short history of the use of iron in the polymerizations, both ROP and condensation. The improvement in the use of iron here has come about in the ROP of LA by using the NHC as a ligand. Reasonably high molar masses are achieved in bulk ROPs, around 50 000 g mol⁻¹, and at around 150 °C good conversion rates were obtained with very low catalyst loadings (1/10 000).

While the use of phosphazenes give excellent control over the stereoselectivity of the ROP of LA,⁷² more recent work has shown that selected NHCs, coupled with a chiral amino(thio) urea and a benzyl alcohol initiator can give 90% conversion after a few hours, and high stereoselectivity.⁷³ This is important as controlling the tacticity of the PLA can modify its degree of crystallinity, and in turn its mechanical and degradative properties. Previously, metals were used to obtain highly isotactic polymers, typified by highly noxious systems Ziegler-Natta catalysts. The ROP of racemic LA can thus yield highly isotactic PLA with high crystallinity and good processibility. In the aforementioned work, they tried several NHCs, with and without the chiral(thio)urea, and while they always obtained quite high conversions in a matter of hours, the best stereo control was obtained with 3 parts of a chiral(thio)urea with 1 part NHC*t*-butyl, giving a high probability of *meso* enchainment (P_m) of 0.93, which is comparable to metal based systems. Typically dispersities were below 1.2, and molecular weights of the order of several tens of thousands.

4 Poly(ethylene oxide)

Here we briefly discuss poly(ethylene oxide) (PEO) given its exceptional importance in the field of drug delivery. Its older name, poly(ethylene glycol) (PEG), is still widely used for lower molecular weight polymers, i.e., below around 10 000 g mol⁻¹, is commonly used in the pharmaceutical and biomedical fields. It is extremely soluble in water, and in general very non-toxic. Its melting point, which can vary from below room temperature to above 60 °C, is highly dependent on the polymer's molecular weight. For the most part extremely safe, and might be considered the standard bearer for polymers in drug delivery, medical applications, pharmaceuticals, and cosmetics, and numerous medical applications. Although it is worth noting that there are exceptionally rare cases of hypersensitivity to PEG that have been found.⁷⁴ IUPAC recommends the name poly(ethylene oxide) when using source-based nomenclature, and poly(oxyethylene) when using structure-based nomenclature, however, the name poly(ethylene glycol) has remained as it hints to the all-important hydroxyl chain-ends, which can have a high impact on the polymer properties, especially when low molecular weights are used. More correctly, one might say, α,ω -dihydroxy-poly(ethylene oxide).⁷⁵ PEG is commonly bound to other compounds through its terminal hydroxyl groups through the process of 'PEGylation', a system widely used to form water dispersible micelles that can encapsulate medication, drugs, proteins etc. too promote transport, and reduce unwanted immunogenicity.⁷⁶ Well publicized uses or example recently in COVID-19 mRNA vaccines produced by

Pfizer/BioNTec and Moderna where it was used to form nanoparticulate lipids to enhance delivery of the SARS-CoV2 antigens.⁷⁷

The synthesis of PEG, and its cousin polyethers poly(propylene oxide), and poly(butylene oxide), have been exceptionally well reviewed by Herzberger *et al.*⁷⁸ and therefore only a short summary appears here. For the most part, the polymers are obtained through ROP of the corresponding epoxide. In the case of PEG, ethylene oxide is polymerised most often with anionic (oxyanionic) and coordination polymerizations, although recent developments have prioritised organic catalysts such as heterocyclic carbenes.

The history of the work is startlingly old. PEG has been known since 1863 when Wurtz polymerized ethylene oxide with a metal hydroxide.⁷⁹ Later, Staudinger followed the polymerization with more explosive results in 1933,⁸⁰ and Flory established a clear idea of the living processes used to make the chains.⁸¹ For the most part, as mentioned above, ethylene oxide has been, and still is, polymerized using alkali metals to support an anionic oxyanion reactive center, with an alkoxide used to provide the starting nucleophilic site of initiation, as shown in Figure 12. This process is extremely sensitive to impurities such as water and air, and if high molecular weights are to be achieved, should be performed under extremely pure conditions in polar solvents such as THF.⁸² Commonly, phase transfer agents, such as crown ethers, of appropriate size to the Cs, K, or Na alkali metals being used are required to ensure solvation of the active chain-ends, although there is considerable evidence that the chain-ends of the polymers themselves can act, pseudo-crown ether like to induce solubilization of the ionic chain-end.⁸³

The polymerization rate constants increase with the increasing size of the counter ion ($\text{Na}^+ < \text{K}^+ < \text{Cs}^+$).⁸⁴ Most commonly, potassium is used, because of the reasonable polymerization results and lower costs (compared to Cs^+). With a lithium counter-ion, the polymerization does not proceed, it being unable to support the larger oxyanion. Although, interestingly, styrene and PEO block copolymers have been shown attainable, as Carlotti *et al.* reported that with tri-isobutyl aluminum added to ethylene oxide, the system was activated enough to allow lithium polystyryl ($\text{PS}^- \text{Li}^+$) to initiate the polymerization towards a PS-PEO block copolymer.⁸⁵

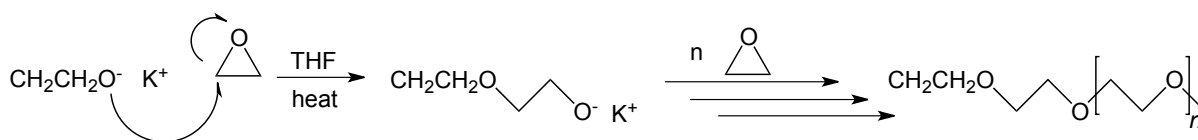


Figure 12. The anionic polymerization of ethylene oxide using an alkali metal and an alkoxide initiator.

Coordination polymerizations of ethylene oxide are particularly useful when trying to target higher molecular weight polymers, with higher melting temperatures and mechanical strengths. Anionic polymerizations are on the whole limited to molar masses below $30\,000\text{ g mol}^{-1}$, and are also slow, often taking days to complete. Coordination polymerizations can reach much higher molecular weights, above several million g mol^{-1} , and are well reviewed by Dimitrov *et al.*⁸⁶ Briefly put, these systems work by using organo-metallic compounds, such as diethyl aluminium zinc oxide coupled with a protic compound that tie the monomer around the metal centre, activating it to polymerization by stabilising the oxyanion.

Future work for PEGs looks likely to concentrate on the development of block copolymers with hydrophobic segments to develop amphiphilic materials that aggregate in a controlled manner in aqueous dispersions. In particular, copolymers with PLA and those that form multi-arm or star-like structures and dendrimers,⁸⁷ are generating much interest to reach a wide number of biomedical applications.⁸⁸ Carboxyl-ester transesterification, to introduce ester segments into polycondensated PEOs is also of interest because it will enhance the biodegradability of the polymer, and decrease the likelihood of retention of PEO in the body, which might otherwise, in very rare cases, lead to hazardous immune responses.⁸⁹

5 Block copolymers from PLA

PLA is hydrophobic and its combination with hydrophilic polymers such as PEG into the same polymer can give rise to an extraordinary range of material properties. Amphiphilic polymers, that is polymers that contain both hydrophilic and hydrophobic blocks that are covalently bound, have been instrumental in creating multifunctional delivery systems and in particular spurring the latest developments in polymer micelles, and nano-capsules. Many examples can be found in the literature where amphiphilic polymers have been used for drug delivery applications.¹ Furthermore, amphiphilic copolymers can be highly varied in their macromolecular structures,⁹⁰ and various reviews and papers demonstrate a wide number of architectures including graft,⁹¹ star-like objects⁹² and brushes of various types and sizes.^{93,94} Their nomenclature is well established by IUPAC.⁷⁵ While the macromolecular structures of these materials heavily impacts on their properties, it should also be noted that the methodology of forming nano-particulates and objects from these materials also determines their final assemblies, with an incredible number of micellar and vesicular architectures being obtained simply by varying these conditions. It should be mentioned also that solvents and co-solvents,⁹⁵ and interestingly, the exploitation of the crystallinity of one of the blocks can strongly impact of these assemblies and the properties of the materials.⁹⁶

The assembly of polymer micelles, shown in Figure 13, is largely explained by the relative interactions between hydrophilic and hydrophobic blocks with each other and the surrounding media. During the micellization process, hydrophobic blocks combine to form the core region, while placing the hydrophilic segment between the core and external aqueous media. Therefore, the hydrophobic core is stabilized by a hydrophilic shell. This unique architecture allows polymer micelles to function as nanoscopic depots or as stabilizers for highly hydrophobic in water insoluble compounds. Unimolecular polymer particles are a class of single molecular micelles that have a nucleus and a covalently linked outer-domain. While micelles are the most common structures, other architectures can arise such as vesicles, worms and so on. The structure that is taken up depends on the types of polymers used, as mentioned above, but also on their molecular weights, respective ratios of hydrophilic and hydrophobic components, and the preparative methods used (for example if co-solvents are used and then washed out with aqueous media).

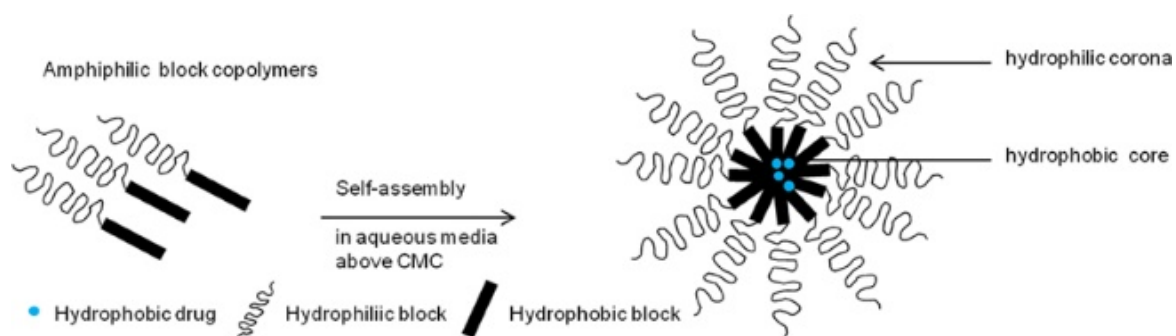


Figure 13. Self-assembly of an amphiphilic block copolymer in aqueous media⁹⁷ (Image reproduced by acknowledging *Frontiers in Pharmacology*).

The development of block copolymer research has remained constant over the last twenty years or so, however, there has been a strong expansion in the development of drug-delivery related studies since 2019.⁹⁸ Interestingly it is not just the type of polymer, but also specific properties that have caught attention, such as dispersity. Low dispersity polymers give much more well defined structures, as demonstrated by a comprehensive review of block copolymer aggregation in dispersions.⁹⁹ Another, extremely comprehensive review by Hasannia *et al.*¹⁰⁰ surveys the structures that block copolymers take up in aqueous solutions, showing how various nanostructures can be formed, including micelles and vesicles such as those in Figure 14. The hydrophobicity, volumetric ratios and tacticities of the hydrophobic and hydrophilic blocks impact heavily on the final types of structures formed and their behaviors. An amazing range of forms exist, with increasingly complex multicompartiment objects being assembled.¹⁰¹ Polymersomes are vesicles, that is, objects that are like sacs with liquids inside and outside, and sizes that can vary from around 40 nm to several microns. They are mostly made of amphiphilic copolymers. Polymersomes are gaining particular interest as the bilayer wall can be used to take on a hydrophobic drug load, and the aqueous interior, a complementary hydrophilic load.¹⁰² Interestingly, low dimensional polymersomes (below 200 nm) can travers biological barriers through pores as they are flexible, however they are more easily damaged than micelles which have a solid, hydrophobic core. The first examples were reported by Eisenberg and colleagues in 1995,¹⁰³ and in our own work, we showed the first examples containing σ -conjugated blocks.^{95,104}

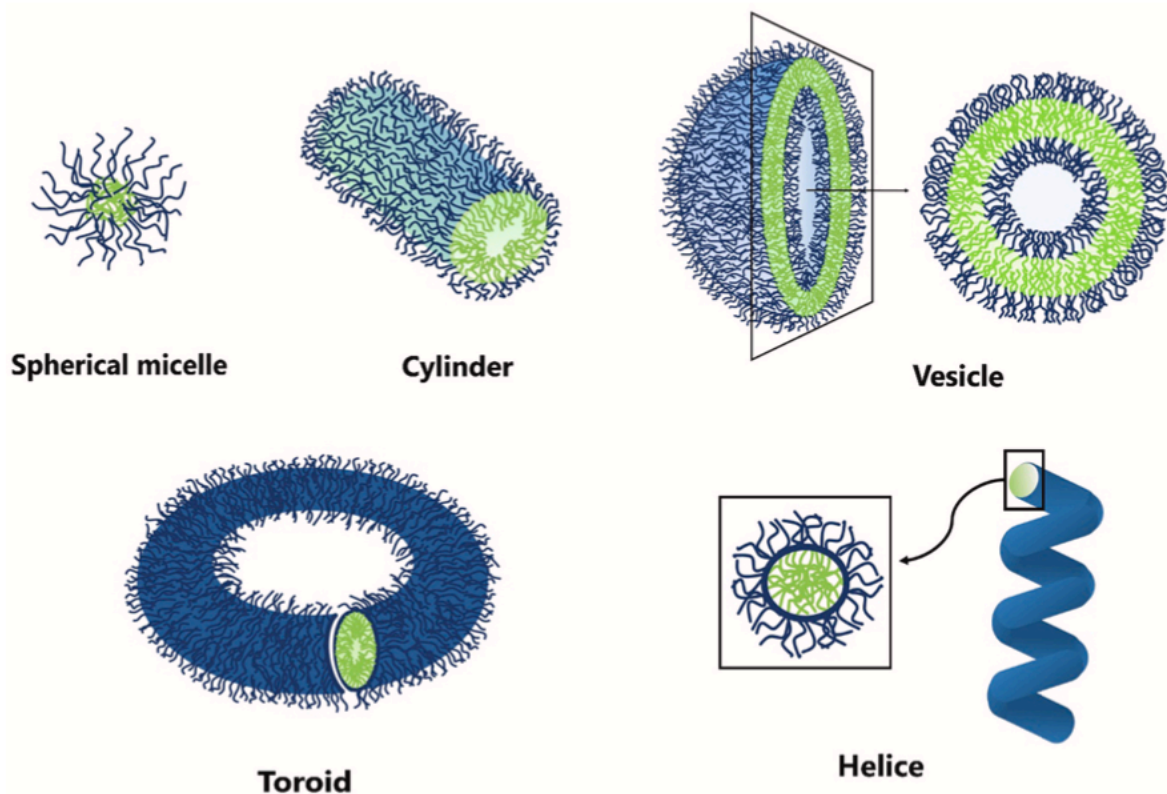


Figure 14. Various structures taken up by amphiphilic block copolymers in aqueous dispersions. Reproduced with permission from Elsevier.¹⁰⁰

The aforementioned review by Hasannia *et al.*¹⁰⁰ also comprehensively covers the syntheses of polymers for polymersomes using ROP, anionic polymerizations, atom transfer radical polymerizations (ATRP),¹⁰⁵ reversible addition-fragmentation chain transfer (RAFT)^{106,107} and polymerization-induced self-assembly (PISA) techniques, therefore this work will not dwell on them, suffice to say that these techniques are extremely useful in preparing polymer blocks with very well controlled, i.e., low dispersities, from a range of vinyl-group carrying monomers, and that PISA greatly facilitates fabrication of polymersomes by using one block as a macroinitiator to form the object *in-situ* while forming the new block.

Here we give a very brief overview of the synthetic routes to block copolymers incorporating PLA, dealing with the main points, and identifying key reviews and papers already published in this field.

The foremost amphiphilic block copolymer incorporating PLA is PLA-*block*-PEG, where PLA and PEG are hydrophobic and hydrophilic blocks, respectively. The drugs can be loaded into the PLA core, or wall, depending on the formed nanostructure, while the PEG allows the objects to remain in the blood stream, resisting elimination by opsonization, that's to say its marking by antibodies and subsequent cellular process of removal termed

phagocytosis. However, a problem with this can be the slow and uncontrolled biodegradation of PLA, thus restricting the dispersal of drugs. Routes to enhance its degradation have been developed, such as the incorporation of synthetic groups, for example labile disulfides, which are environment sensitive and breakdown on exposure to the reductive environment common to cells. This area has been very well reviewed by Bawa and Oh¹⁰⁸ in 2017, where they focus on the concept of a ‘stimuli-responsive platform’ has been developed to improve the release of drugs. Particularly interesting is the use of acidic pH responsive groups, such as imines, orthoesters, acetals and ketals, which in proximity to tumour tissue, which has a lower pH at around 6.5 to 6.9, can break down and enhance drug off-loading. These groups can be made pendent, mid-block or a range of locations on the polymer chains. This coupled with chemotherapeutics makes for a powerful delivery system,¹⁰⁹ as these small molecule drugs are commonly highly hydrophobic and would otherwise be unable to reach the tumours, but can also be extended to delivering oligonucleotides, proteins, and messenger RNAs (mRNAs), etc. Figure 15, prepared by Avramović *et al.*,¹⁰⁹ well illustrates the way in which drugs and stimuli sensitive systems can be combined in micelles, using techniques which can be clearly extended to other nano-objects such as vesicles. While PLA commonly occupies the central core, the use of poly(ϵ -caprolactone) (PCL) and poly[lactic-*co*-(glycolic acid)] (PLGA), amongst many others, is also widespread, while the drugs most commonly followed for anti-cancer use are doxorubicin (DOX) and metformin (Met). Reference 97 is a particularly clear review of the way in which polymer micelles can be used for drug delivery, while reference 110 deals with their use for cancer treatments.

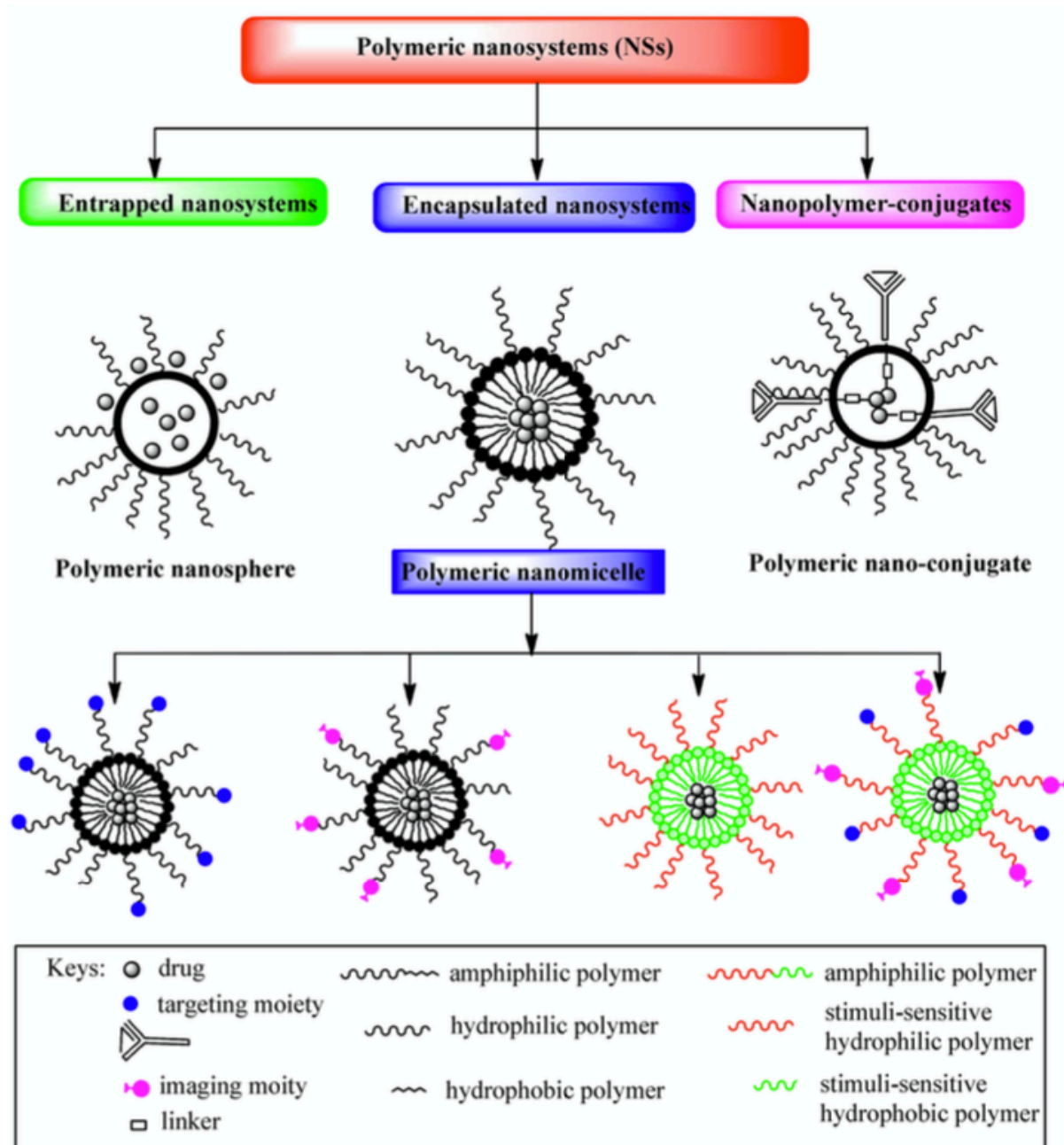


Figure 15. Incorporation of drugs and environmentally sensitive elements into nanoscale micelles. Image reproduced from reference 109 courtesy of MDPI.

One should not forget of course that these materials can also be used to make hydrogels, either through the incorporation of crosslinking groups, or by using higher molecular weight polymer which limits the material's dispersion into the blood stream. The first example was prepared in 1997 by Jeong *et al.*¹¹¹ The use of pegylated PLA as an injectable gel has been well reviewed,^{112,113} as have the analogous PLGA block copolymers for anticancer treatments.¹¹⁴ The hydrogel supports the steady release of drugs such as doxorubicin to a localized site, again with the PEG segments decreasing immunological recognition to increase times in the body up to several weeks. Further modifications, for example with folic acid, can

further enhance site-specificities. Interestingly, the incorporation of urethane groups can also enhance shape-memory effects for the gel.

Other qualities can be brought into play, for example, with PLGA its crystallinity, strength, and degradation can be influenced by varying the degree of lactide units, as these carry the hydrophobic methyl groups which repel water, braking ester degradation. Furthermore, the choice of whether to use (*R,R*)-lactide (D-lactide) or (*S,S*)-lactide (L-lactide) can give highly amorphous or crystalline copolymers, respectively. It is worth noting that even the type of storage and age of the polymer can influence its properties. Overall, these properties will also decrease with a reduction in molecular weight.

The breakdown of the PLA segments, and the subsequent fate of the PEG block has been followed by studies in rats, which identified that the copolymer was distributed to the spleen, liver, and kidney.¹¹⁵ The PEG-*block*-PLA itself is not cleared renally, due to the lipophilicity of the PLA component, but rather the PLA is metabolized and the PEG-metabolite is eliminated in urine, with around 80% removed with 48 h. An excellent review of the extent of drug release from these biodegradable polymers appeared in 2021.¹¹⁶

With respect to the synthesis of PEG-*block*-PLA, Zhu *et al.*'s paper exemplifies the typical technique.¹¹⁷ Monomethoxy-PEG, i.e., PEO with one end capped by a methoxy group and the other a labile hydroxy group is used as a mono-initiator in a ROP of LA in a solid melt with SnOct₂. The reaction here was performed at 140 °C for 72 h, and the product recovered by dissolving in DCM and precipitating into cold diethyl ether. The drug can be incorporated into the micelles, for example, by dissolving both the drug and the PEG-*block*-PLA into THF, and then by the slow addition of water, to force the formation of drug-containing micelles.

One problem with this technique is of course that the process only delivers rather low concentrations of nano-objects, and of more concern for industrialisation, is rather uncontrollable, resulting in various structures. The use of the aforementioned PISA technique has been of interest, as it decreases the volume of solvent involved. More recently,¹¹⁷⁸ crystallisation of the blocks during the preparation of the block copolymers has been explored, as this can push towards greater anisotropy and, thus, better organised structures. The reaction shown in Figure 16 was carried out in toluene with a triazabicyclodecene catalyst,¹¹⁹ with the classic monomethoxy-PEG initiator. Importantly the reaction achieves high conversions after even 90 seconds (most likely at room temperature although this was not explicit), and drives towards the formation of fibers and lamellae. The polymerization is most likely catalyzed by the activation of lactides through the use of the aminated organo-catalysts, which maintain the

possibility of further chain extensions, although transesterifications can occur should the reactions be left for too long.

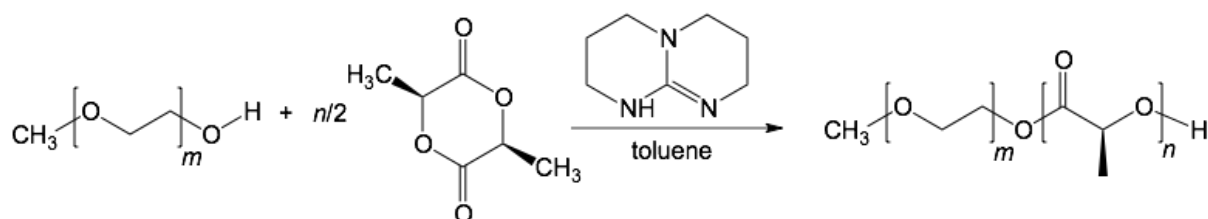


Figure 16. ROP of L-lactide performed in toluene with triazabicyclodecene catalyst. Adapted from reference 120.

PLA has of course been polymerized with other blocks, as indicated above, but not all examples are amphiphilic. PLA copolymers with blocks that are miscible such as poly(2-isopropyl-2-oxazoline) have been prepared.¹²¹ Both polymers are semi-crystalline, but nevertheless here display a single T_g . The up-shot is that the crystallization of PLA is modified, and confirms that fine tuning of its properties, such as with PLGA, can be attained with additional, miscible segments. The synthesis of this material is particularly interesting, being performed from an ethyne-carrying alcohol to initiate the ROP of the lactide monomer with SnOct_2 , to be subsequently clicked with the azide group at the chain-end of the poly(2-isopropyl-2-oxazoline). An alternative route to block copolymers was that published by Caillol *et al.*,¹²² in which PLA was copolymerized with *N*-carboxyanhydride modified with benzyl glutamate units – thus lending peptide units to copolymer to accelerate biodegradation.

A massive range of copolymers are available through modification of the hydroxyl group at the chain-end of the PLA to groups that can be used for NMP, RAFT and ATRP polymerizations,¹²³ and exemplified by Figure 17. The review by Mays and colleagues puts NMP, RAFT and ATRP well into perspective, and for further details the reader is directed there.¹²⁴ Furthermore these materials' use in drug delivery systems, including copolymers with poly(*N*-vinylpyrrolidone) (PNVP), poly((2-methacryloyloxy)ethyl phosphorylcholine) (PMPC), and poly(*N*-(2-hydroxypropyl)methacrylamide) (PHPMA) is reviewed by Gigmes and Trimaille.¹²⁵ These materials can have exceptionally well-tuned dispersities, thus making for precision nano-architectures, however, there remains some concern over the use of ethylene-based main-chains which reduces their biodegradability.

Another area outside of the scope of this work is the aforementioned polymerization-induced self-assembly (PISA) technique, in which the polymerization drives the organization

of macromolecules to give nanoparticles *in-situ*, occurring in the polar and non-polar media, which is well reviewed by Cornell *et al.*¹²⁶

Much remains to be discovered though. Interesting work using an indium catalyst makes possible the sequential, one pot polymerization of methyl methacrylate and lactides without resorting to a pre-modification of the PLA chain-ends, due to the ability of the catalyst to activate both reactions, as also shown in Figure 17.¹²⁷ Working at relatively low temperatures, at 100 °C or below, the catalyst can attain good molecular weights (M_n), even above 100 000 g mol⁻¹ with dispersities generally near or below 1.6. The mechanism is understood to be via an alkyl or alkoxide coordination and insertion polymerization for the LA, while the MMA is through an alkyl or alkoxide conjugated Michael addition.

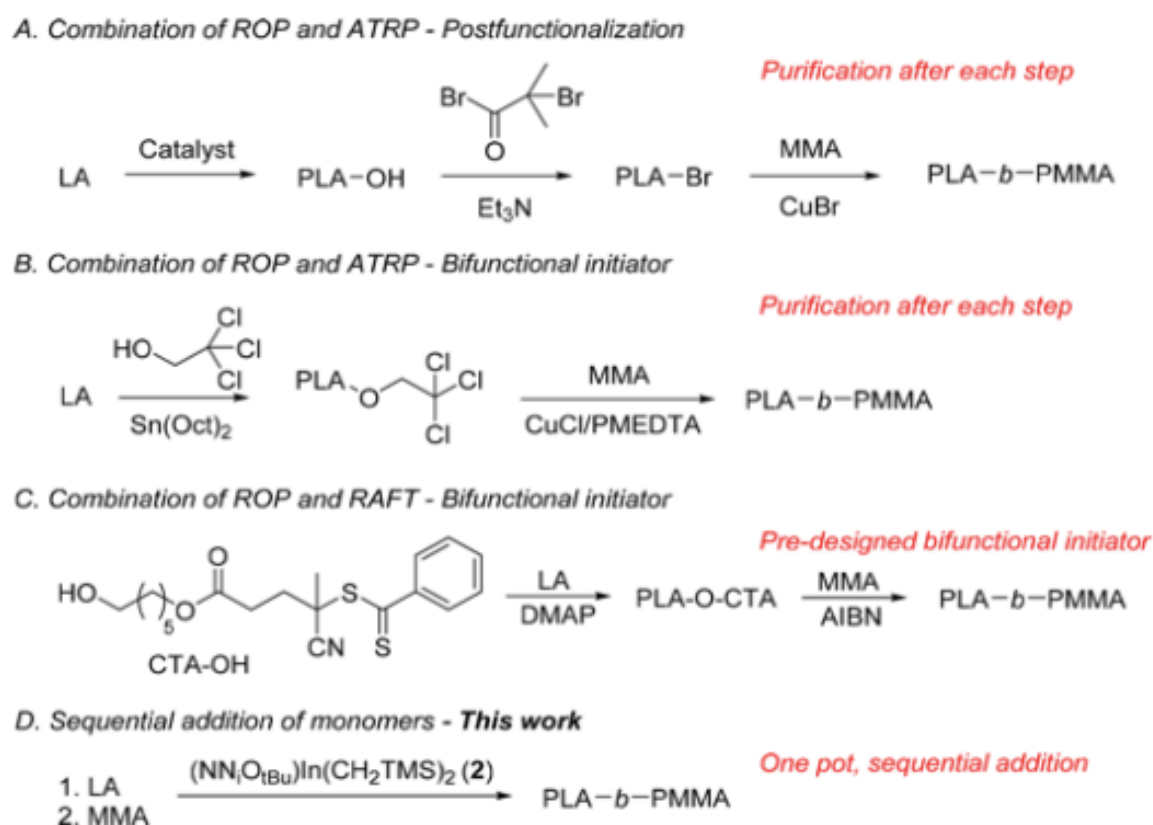


Figure 17. Comparison the required steps for the formation of PLA-*block*-PMMA copolymers using ATRP, RAFT or an indium-based catalyst. Reprinted with permission from Jung *et al.*¹²⁷ 2020 Copyright ACS.

An alternative method of polymerizing MMA and LA is demonstrated by the fine work by Taton and colleagues, where they employ a trimethylsiloxy initiator with 1-*tert*-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylideneamino]-2λ⁵,4λ⁵-

catenadi(phosphazene), or P4-*t*-Bu for short to polymerise MMA and then LA in THF in the same pot.¹²⁸ Incidentally, they also give an excellent review of acrylate and lactide copolymerizations.

More complex, non-linear copolymers can also be made for drug delivery systems. Recent work combines PLA and poly((oligoethylene glycol) methyl ether acrylate) to generate stars as shown in Figure 18.¹²⁹ Stars have been found to be particularly good at forming micelles and core-shell structures with small hydrodynamic volumes and unique spherical structures, and demonstrate a good functionality at their surfaces when compared to linear block copolymers. In their work, Oliveira *et al.* use ATRP but, conscious that the copper catalyst is toxic with respect to drug delivery at regular concentrations (>20 000 ppm), they have used continuous activator regeneration (ACAR) to rejuvenate the metal in ATRP, and hence reduce the metal down to an extraordinarily low 1070 ppm! They were thus able to prepare 4-*star*-PLA-*block*-POEOA copolymers, where POEOA is poly[(oligoethylene glycol) methyl ether acrylate].

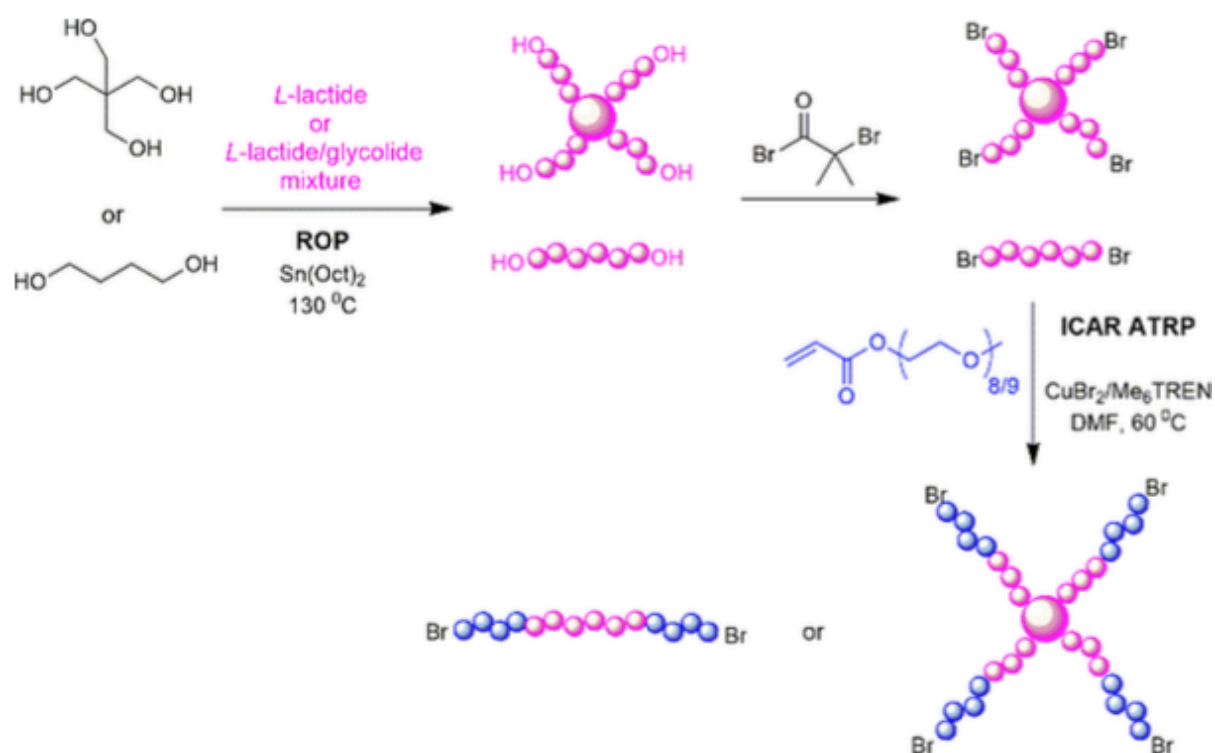


Figure 18. ROP and ATRP used to prepare amphiphilic 4-*star*-PLA-*block*-poly[(oligoethylene glycol) methyl ether acrylate] copolymers. Reproduced with permission from the RSC.¹²⁹

Extending to six arms is possible, for example, using dipentaerythritol as a core, and with PLA and PCL. Well-defined structures are possible when using ROP, and most-likely

arising from the macromolecules' multi-directional covalency, a three-fold improvement in tensile toughness. Most interesting in this was the use of DBU to perform the ROP at below 40 °C, in toluene for 8 h, generating molecular weights (M_n) in the tens of thousands and reasonable dispersities around 1.3.¹³⁰

An excellent review that recently appeared, that considers in-depth the impact of using tri-block, star-like and more complex skeletal structures for drug delivery.¹³¹ The use of surfactants with these materials also raises the possibility of personalized medicines.

Finally, it is worth mentioning the formation of PLLA microparticles and microcapsules for drug delivery. An excellent review considers the development of methodologies in this area including microfluids and electrospraying.¹³²

6 Modelling

The use of computational chemistry, to be distinguished from theoretical chemistry, is often perceived by experimenters as a means of prediction, with all that this implies in terms of saving time and prospecting, but also as a routine tool. In the latter case, it might be in the same way as an experimental technique to allow the interpretation of pre-established measured data.

Before explaining the various modeling tools adapted to the delivery of drugs linked to polymers, the modeler would like to speak of a 'computational strategy', and appropriately, it is necessary to recall what are the main challenges offered to modeling in this area. This is, on the one hand, the need to access the description of the physico-chemical properties and the reactivity of molecules¹³³ and, on the other hand, to access the description of the structural properties of formulation materials.¹³⁴

It is quite obvious that these two fields of research do not call upon the same modelling tools; especially because the dimension of the chemical problems are not the same. Any computational chemistry modeler knows how the number of atoms that it is necessary to take into account in a given problem will condition both the calculation time and the precision that she or he is able to obtain in the final result. Indeed, the various algorithms existing in computational chemistry all depend on the explicit resolution of the Schrödinger equation or of physics equations based on more or less strong and controlled approximations and which all depend directly on the number of terms it will be necessary to calculate: which amounts roughly to considering that it depends on the number of atoms. Several solutions are known to overcome this problem, such as the more or less empirical and parameterized methods of classical molecular dynamics¹³⁵ of Monte Carlo (stochastic algorithm¹³⁶) or the coarse grain methods (Figure 19).¹³⁷

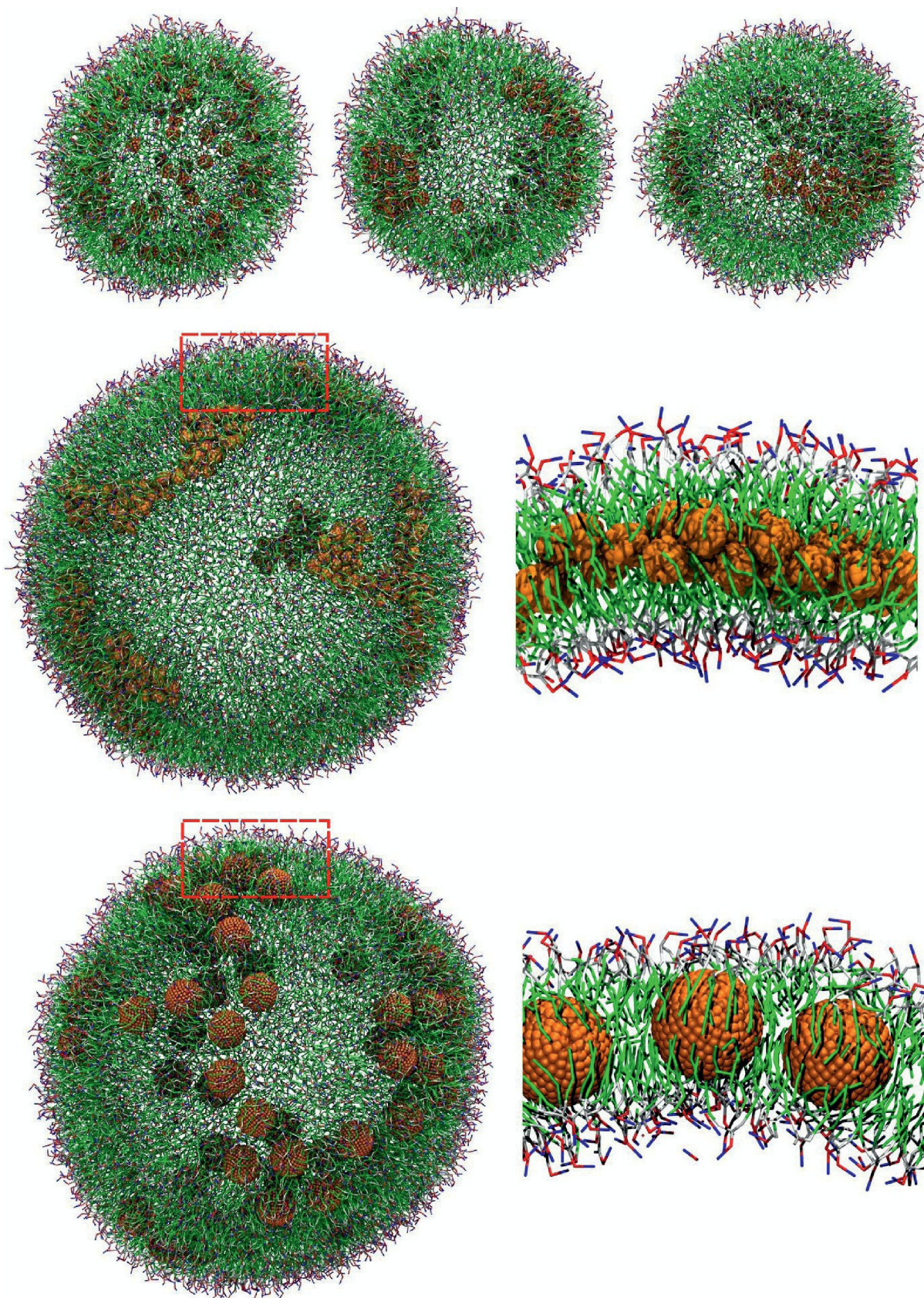


Figure 19. The self-assembling process of 100 fullerenes with a liposome made of 1512 DMPC lipid molecules, reproduced with permission from Elsevier.¹³⁷

On the other hand, it is necessary to remember that in the case where these methods are used, the chemist will not be able to access the electronic information which is necessary to predict and / or interpret the physicochemical properties of the molecules present. At the most, it will be able to obtain structural information which, as we have just recalled, nevertheless represents one of the two major fields of active research in the field of drug delivery. In recent years, alternative solutions involving, in particular, the use of reactive force fields have allowed modelers to combine the advantages of molecular dynamics approaches and more or less quantum approaches in order to access information on the formation and breaking of chemical bonds involved in the reactivity of the systems studied.^{138,139}

To want, in a few lines, to summarize the progress and advances in modeling in the field of drug delivery is illusory. There are several reviews focused on these computational aspects that it is necessary to know, and which will allow the reader to effectively situate each of the approaches which have just been recalled in the context of drug delivery.¹³⁹⁻¹⁴¹ However, we think it necessary to come back briefly to the notion of computational strategy mentioned above because, ultimately, it is this choice that depends on the very usefulness of the models and in particular in the field of the biocompatible polymers used for drug delivery. The capacity of computing has increased dramatically over the past decade. It is, of course, no stranger to the routine use of computational methods and to the diversification of computational strategies (and / or experience-theory coupling strategy) in studies dedicated to computer-aided drug design. Who would have imagined, if only 20 years ago, that we would be able to model systems comprising thousands of atoms as in drug @ MOF (metal-organic framework) encapsulated in polymeric matrices by means of simulations?¹⁴² Would we have thought to be able to model the influence of the terminations of hyperbranched (branched) polymers to understand the spatial arrangement of these polymers which is a, if not the key point to understand their role in the administration of drugs?¹⁴³

Access to the software in which the modelling algorithms are implanted is another reason why these calculations are multiplying nowadays. Added to this is the fact that modelling, as costly as it may be, allows access to a large number of data, calculated on a more or less important variety of reagents, in times which are incommensurate with the times linked to a synthesis. Modelling is undoubtedly a precious help to allow experimenters to rough up and guide their choices on the most effective reagent(s) and even more on those which are the least effective because, in fine, knowing that a compound or a family of compounds is not suited to a desired response allows the experimenter to save precious time.¹⁴⁴

As has just been recalled, modeling is only useful when it allows access to a large number of data even if these are only obtained with a more or less low degree of precision. Indeed, it is often more useful to access the comparison at the same level of calculation i.e., at the same level of error, of two properties or of the same physicochemical quantity on two different systems rather than to seek to estimate some. the most precise possible value of this property^{145,146} The majority of the computational strategies implemented to date in the field of drug delivery are very clearly placed in this approximation framework¹⁴⁷ and ligand docking.¹⁴⁸

This given, how can we not ask the question about the legitimacy of these models obtained on systems comprising several thousand atoms and obtained within the framework of details impacted by such dimensions, especially when we compare these models to those carried out in quantum chemistry on very small molecular systems never comprising more than 20 atoms and for which it is sometimes so complicated to properly describe the mechanisms involved?¹⁴⁹ This question seems legitimate for two reasons. On the one hand because we know how much the description of the physicochemical and spectroscopic properties requires computational precision in order to reproduce, at a minimum, usual spectral data such as UV-visible, infra-red, NMR. On the other hand, because, as stated by Bunker¹⁵⁰ we must not lose sight of the fact that the main challenge that awaits the modelers of tomorrow in the field of drug delivery is at the level of 'the design of drug delivery mechanisms'. Strictly speaking, these two fields require much more precision than those mainly useful for the calculation of the structural properties of formulation materials. If we come back to the example cited above for the smallest systems, the authors show the extent of the challenge that awaits modelers and how useful it will be to make the right choices in terms of computational strategies and uses of quantum tools (or other) including among those perfectly honed such as those of DFT,¹⁵¹ which may ultimately turn out to be from time to time unsuitable, not to say misleading.¹⁵² We therefore leave the reader to imagine what less precise, more empirical or refined methods such as those using for example "parameterized" or coarse-grained force fields may yield for the future study of the reaction mechanisms of drug delivery. It is mainly these pitfalls that still lead modelers to favor more 'quantum' computational strategies on systems of reduced dimensions¹⁵³⁻¹⁵⁶ supposed to contain all the chemistry / reactivity of the problem and on which it is easy and inexpensive to implement all kinds of corrections to the models used, i.e., such as the influence of the ambient medium / solvent (PCM model)¹⁵⁷ and inform that the corrections for long-range effects in the case of DFT approaches.^{158,159} Finally, let us note, to finish this non-exhaustive panel of approaches dedicated to drug delivery, the existence of other strategies which continue to be promising such as hybrid approaches of the QM / MM type

such as the approaches of Car – Parrinello / Molecular Mechanics MD¹⁶⁰ and Empirical Valence Bond¹⁶¹ whose qualities and limitations have been known for more than twenty years¹⁶¹ and purely mathematical approaches.¹⁶³

7 Conclusion

This teacherly review introduced the range of synthetic routes available to preparing PLA and its block copolymers used for drug delivery systems. It is hoped that it will enable an easy access to this exciting and fast developing field. There are many challenges in this field, especially for the release of drugs and synthetic materials that are non-toxic, biodegradable and biocompatible, all while retaining a precision-based polymerization system. The combination of this, with drugs and surfactants raises the exciting possibility of drug delivery systems that will be tailored to the needs of individuals rather than providing bulk preparations for all people.

Acknowledgements

We wish to kindly thank FAPESP (Grant number FAPESP 2020/11440-5) for their support of PCT during the preparation of this manuscript.

References

- 1 Ruiz ME and Montoto S, Routes of Drug Administration. In: Talevi A, Quiroga PAM, editors. *ADME Processes in Pharmaceutical Sciences*. Cham: Springer International Publishing, 97–133 (2018).
- 2 Chang R-K, Raw A and Lionberger R, Yu L, *AAPS J* **15**: 41–52 (2012).
- 3 Holzapfel BM, Reichert JC, Schantz JT, Gbureck U, Rackwitz L, Nöth U, *et al. Adv Drug Deliv Rev* **65**: 581–603 (2013).
- 4 Mosley RJ, Hart J, Davis KL, Wower J and Byrne ME, *Langmuir* **38**(5): 1698 (2022).
- 5 Serna N, Pallarès V, Unzueta U, Garcia-Leon A, Voltà-Durán E, Sánchez-Chardi A, Parladé E, Rueda A, Casanova I, Falgàs A, Alba-Castellón L, Sierra J, Villaverde A, Vázquez E, Mangues R, *J. Controlled Release*, **343**: 277 (2022).
- 6 Pola R, Vícha M, Trousil J, Grosmanová E, Pechar M, Rumlerová A, Studenovský M, Kučerová E, Ulbrich P, Vokatá B and Etrych T, *Pharmaceutics* **15**(2): 406 (2023).
- 7 Liu B, Singh K, Gong S, Canakci M, Osborne BA and Thayumanavan S, *Angew. Chem. Int. Ed* **60**: 12813 (2021).
- 8 Jantzen GM and Robinson JR, Sustained and controlled release drug delivery systems, in *Modern Pharmaceutics*, Fourth Edition, 747-789 (2002).
- 9 Azzam T and Domb AJ, *Curr Drug Deliv* **1**: 165–93 (2004).
- 10 Coelho JF, Ferreira PC, Alves P, Cordeiro R, Fonseca AC, Góis JR, *et al., EPMA J* **1**: 164–209 (2010).
- 11 Chen Y, Geever LM, Killion JA, Lyons JG, Higginbotham CL and Devine DM, *Polymer-Plastics Technology and Engineering* **55**(10): 1057-1075 (2016).
- 12 Casalini T, Rossi F, Castrovinci A and Perale GA, *Front Bioeng Biotechnol* **7**: 259 (2019).
- 13 Saini P, Arora M and Kumar MNVR, *Advanced Drug Delivery Reviews* **15**: 47-59 (2016).
- 14 Oliver-Ortega H, Tarrés Q, Mutjé P, Delgado-Aguilar M, Méndez JÁ and Espinach FX, *Polymers* **12**: 2144 (2020).
- 15 Castro-Aguirre E, Iñiguez-Franco F, Samsudin H, Fang X and Auras R, *Advanced Drug Delivery Reviews* **107**: 333-366 (2016).
- 16 Stefaniak K and Masek A, *Materials* **14**: 5254 (2021).
- 17 Brzeziński M and Basko M, *Molecules* **28**: 1386 (2023).
- 18 Jem KJ and Tan B, *Advanced Industrial and Engineering Polymer Research* **3**(2): 60-70 (2020).
- 19 Cisneros K, Chowdhury N, Coleman E, Ferdous T, Su H, Jennings JA, Bumgardner JD, Fujiwara T, *Macromol Biosci* **21**: 2100123 (2021).
- 20 Jelonek K, Kaczmarczyk B, Orchel A, Chodurek E, Jaworska-Kik M, Padaszyński P, Bębenek E, Chrobak E, Musiał-Kulik M, Foryś A, Boryczka S, Li S and Kasperczyk J, *Journal of Drug Delivery Science Technology* **65**: 102707 (2021).
- 21 Ghasemi S, Ahmadi L and Farjadian F *J Mater Sci* **57**: 17433 (2022).
- 22 Da Costa D, Exbrayat-Héritier C, Rambaud B, Megy S, Terreux R, Verrier B and Primard C, *J Nanobiotechnol* **19**: 12 (2021).
- 23 Moezzi M, Sa'di V, Ranjbar-Mohammadi M, Saghafi R and Barez F, *The Journal of The Textile Institute*, DOI: 10.1080/00405000.2022.2145450 (2022).
- 24 da Silva D, Kaduri M, Poley M, Adir O, Krinsky N, Shainsky-Roitman J, Schroeder A, *Chemical Engineering Journal* **340**: 9 (2018).
- 25 Liu W, Wei J and Chen Y, *New J Chem* **38**: 6223–9 (2014).
- 26 Zhu W, Liu S, Zhao J, Liu S, Jiang S, Li B, *et al., Acta Biomaterialia* **10**: 3018–28 (2014).

- 27 Campana PT, Marletta A, Piovesan E, Francisco KJM, Neto FVR, Petrini L, Silva TR, Machado D, Basoli F, Oliveira Jr, ON, Licoccia S and Traversa E, *Bull Chem Soc Jpn* **92**: 1237–1244 (2019).
- 28 Lu L and Mikos AG, Poly(lactic acid), in: Mark JE (Ed.) *Polymer Data Handbook*, Oxford University Press, New York, 627-633 (1999).
- 29 Pretula J, Slomkowski S and Penczek S. *Advanced Drug Delivery Reviews* **107**: 3–16 (2016).
- 30 Masutani K, Kimura Y. Chapter 1. PLA Synthesis. From the Monomer to the Polymer. In: Jiménez A, Peltzer M, Ruseckaite R (ed). *Polymer Chemistry Series*. Cambridge: Royal Society of Chemistry 2014; 1–36.
- 31 Fan Y, Nishida H, Shirai Y and Endo T, *Polymer Degradation and Stability* **84**: 143–149 (2004).
- 32 Shinno K, Miyamoto M, Kimura Y, Hirai Y and Yoshitome H, *Macromolecules* **30**: 6438-44 (1997).
- 33 Vert M, Chen J, Hellwich K-H, Hodge P, Nakano T, Scholz C, Slomkowski S and Volhidal J, **92**(1): 193-211 (2020).
- 34 Yi W-J, Li L-J, Hao Z, Jiang M, Lu C, Shen Y and Chao Z-S, *Ind Eng Chem Res* **56**(16): 4867-4877 (2017).
- 35 Shen J, Wei RQ, Liu Y, Liu XN and Zhong Y, *Advanced Materials Research* **152–153**: 222–228 (2010).
- 36 Pires M, Murariu M, Cardoso AM, Bonnaud L and Dubois P, *Polymer Bulletin* **77**: 2111-2137 (2020).
- 37 Carrasco F, Pagès P, Gámez-Pérez J, Santana OO and Maspoch ML, *Polymer Degradation Stability* **95**: 2508-2514 (2010).
- 38 Ajioka M, Enomoto K, Suzuki K and Yamaguchi A, *Bull Chem Soc Jpn* **68**: 2125-2131 (1995).
- 39 Moon S-I, Lee C-W, Taniguchi I, Miyamoto M and Kimura Y, *Polymer* **42**: 5059-5062 (2001).
- 40 Takenaka M, Kimura Y and Ohara H, *Polymer* **126**: 133–140 (2017).
- 41 Hu Y, Daoud WA, Cheuk KKL and Lin CSK, *Materials* **9**: 133 (2016).
- 42 Singh SK, Anthony P and Chowdury A, *Oriental Journal of Chemistry*, **34**: 1984-1990 (2018).
- 43 Balla E, Daniilidis V, Karloti G, Kalamas T, Stefanidou M, Bikiaris ND, Vlachopoulos A, Koumentakou I and Bikiaris DN, *Polymers* **13**(11): 1822 (2021).
- 44 Dopp E and Rettenmeier AW, Tin, Toxicity. In: Kretsinger R.H., Uversky V.N., Permyakov E.A. (eds) *Encyclopedia of Metalloproteins*. Springer, New York, NY (2013). https://doi.org/10.1007/978-1-4614-1533-6_118
- 45 Blunden S and Wallace T, *Food and Chemical Toxicology* **41**(12): 1651-1662 (2003).
- 46 Jenkins SM, Ehman K and Barone Jr S, *Developmental Brain Research* **151**(1-2): 1-12 (2004).
- 47 da Silva IF, Freitas-Lima LC, Graceli JB and de Melo Rodrigues LC, *Front Endocrinol* **8**: 366 (2018).
- 48 Bakibaec AA, Gazaliev AM, Kabieva SK, Fedorchenko VI, Gub GY, Smetanina EI, Dolgov IR and Gulyaev RO, *Procedia Chemistry* **15**: 97-102 (2015).
- 49 Hwang SY, Oh DYX and Park JY, *Key Engineering materials* **773**: 25–29 (2018).
- 50 Lyubov D, Tolpygin AO and Trifonov AA, *Coordination Chemistry Reviews* **392**: 83-145 (2019).
- 51 Topham P, Use of Non-isothermal DSC in Comparative Studies of Tin(II) Systems for the Ring-Opening Polymerization of D- lactide, *Polymer International*: same series as this paper (2023).

- 52 Duda A and Penczek S, Mechanism of aliphatic polyester formation. In Biopolymers, Vol. 3b: Polyesters II. Properties and Chemical Synthesis, Steinbüchel A and Doi Y (Eds.), Wiley-VCH, Weinheim (2002), pp. 371-429.
- 53 Balla E, Daniilidis V, Karloti G, Kalamas T, Stefanidou M, Bikiaris ND, Vlachopoulos A, Koumentakou I and Bikiaris DN, *Polymers* **13**(11): 1822 (2021).
- 54 Ryner M, Stridsberg K, Albertsson A-C, von Schenck H and Svensson M, *Macromolecules* **34**: 3877–3881 (2001).
- 55 Pholharn P, Srithep Y and Morris J, *IOP Conf. Series: Materials Science and Engineering* **213**: 012022 (2017).
- 56 Nishida H, Mori T, Hoshihara S, Fan Y, Shirai Y and Endo T, *Polymer Degradation and Stability* **81**: 515–23 (2003).
- 57 Cicero JA, Dorgan JR, Dec SF and Knauss DM, *Polymer Degradation and Stability* **78**: 95-105 (2002).
- 58 Sirisinha K and Samana K, *J Appl Polym Sci* **138**(10): 49951 (2021).
- 59 Byers JA, Biernesser AB, Delle Chiaie KR, Kaur A and Kehl JA, *Adv Polym Sci* **279**: 67–118 (2018).
- 60 D'Auria I, D'Alterio MC, Tedesco C and Pellicchia, *RSC Adv*, **9**: 32771 (2019).
- 61 Lee C and Hong S, *Mod Chem Appl* **2**(4): 1000144 (2004).
- 62 Boileau S and Illy N, *Progress in Polymer Science* **36**: 1132–1151 (2011).
- 63 Jones GO, Chang YA, Horn HW, Acharya AK, Rice JE, Hedrick JL, *et al.*, *J Phys Chem B* **119**: 5728–37 (2015).
- 64 Chang YA and Waymouth RM, *Polym Chem.***6**: 5212–8 (2015).
- 65 Baško M and Kubisa P, *J Polym Sci A Polym Chem* **48**: 2650–8 (2010).
- 66 Peres C, Matos AI, Connot J, Sainz V, Zupančič E, Silva JM, *et al.*, *Acta Biomaterialia*. **48**: 41–57 (2017).
- 67 Connor EF, Nyce GW, Myers M, Mòck A and Hedrick JL, *J. Am. Chem. Soc.*, **124**: 914 (2002).
- 68 Fèvre M, Pinaud J, Gnanou Y, Vignolle J, and Taton D, *Chem Soc Rev*, **5**: 2142 (2013).
- 69 Mezzasalma L, Dove AP, Coulembier O, *Eur Polym J* **95**: 628–634 (2017).
- 70 Mincheva R, Murthy Chilla SN, Todd R, Guillerm B, De Winter J, Gerbaux P, Coulembier O, Dubois P and Raquez J-M, *Polymers* **11**: 1987 (2019).
- 71 Nylund PVS, Monney B, Weder C and Albrecht M, *Catal Sci Technol*. **12**(3): 996 (2022).
- 72 Zaky MS, Wirotius AL, Coulembier O, Guichard G and Taton DA, *Chem. Commun.* **57**: 3777–3780 (2021).
- 73 Zaky MS, Wirotius A-L, Coulembier O, Guichard G, Taton D, *ACS Macro Lett.* **11**: 1148 (2022).
- 74 Shi D, Beasock D, Fessler A, Szebeni J, Ljubimova JY, Afonin KA and Dobrovolskaia MA, *Advanced Drug Delivery Reviews*, **180**: 114079 (2022).
- 75 Hiorns RC, Boucher RJ, Duhlev R, Hellwich K-H, Hodge P, Jenkins AD, *et al.*, *Pure and Applied Chemistry* **84**: 2167–2169 (2012).
- 76 Turecek PL, Bossard MJ, Schoetens F and Ivens IA, *Journal of Pharmaceutical Sciences* **105**: 460-475 (2016).
- 77 Thi TTH, Pilkington EH, Nguyen, Lee, JS, Park KD and Truong NP, *Polymers*, **12**(2):298 (2020).
- 78 Herzberger J, Niederer K, Pohlit H, Seiwert J, Worm M, Wurm FR and Frey H, *Chemical Reviews* **116**(4): 2170 (2016).
- 79 Wurtz CA, *Ann Chim Phys* **69**: 317 (1863).
- 80 Staudinger H and Lohmann H. *Justus Liebigs Annalen der Chemie* **505**: 41–51 (1933).
- 81 Flory PJ, *J Am Chem Soc* **62**: 1561–1565 (1940).
- 82 Beaudoin E, Hiorns RC, Borisov O and François J, *Langmuir* **19**: 2058 (2003)

- 83 Penczek S, Cypryk M, Duda A, Kubisa P and Słomkowski S, *Prog Polym Sci* **32**: 247–282 (2007)
- 84 Esswein B and Möller M, *Angewandte Chemie International* **35**: 623–625 (1996).
- 85 Carlotti S and Peruch F, Cyclic Monomers: Epoxides, Lactide, Lactones, Lactams, Cyclic Silicon-Containing Monomers, Cyclic Carbonates, and Others In: Hadjichristidis N, Hirao A, ed. *Anionic Polymerization: Principles, Practice, Strength, Consequences and Applications*. Springer, Japan pp. 191–305 (2015).
- 86 Dimitrov I and Tsvetanov CB, in *Polymer Science: A Comprehensive Reference*; Vol. 4, 551–569, Penczek S and Grubbs RH, Eds: Matyjaszewski K and Möller M, Series Eds, Elsevier, Amsterdam, 2012.
- 87 Feng XS, Taton D, Chaikof EL and Gnanou Y, *J Am Chem Soc* **127**: 10956 (2005).
- 88 Kubisa P, Lapienis G and Biela T, *Polym Adv Technol* **32**: 3857 (2021)
- 89 Cai Q, Li X and Zhu W, *Macromolecules* **53**: 2177 (2020).
- 90 Wang Y and Grayson SM, *Adv Drug Deliv Rev* **64**: 852–865 (2012).
- 91 Bhattacharya A and Misra BN, *Progress in Polymer Science* **29**: 767–814 (2004).
- 92 Yang C, Liu SQ, Venkataraman S, Gao SJ, Ke X, Chia XT, *et al.*, *J Control Release* **208**: 93–105 (2015).
- 93 Gao H and Matyjaszewski K *J Am Chem Soc* **129**: 6633–6639 (2007); (b) Zhang YY, Li Y, Zhou XJ, Zhang XH, Du B-Y and Fan ZQ, *Macromolecular Rapid Communications* **36**: 852–857 (2015).
- 94 Song DP, Lin Y, Gai Y, Colella NS, Li C, Liu X-H, *et al.*, *J Am Chem Soc* **137**: 3771–3774 (2015).
- 95 Sommerdijk NAJM, Holder SJ, Hiorns RC, Jones RG and Nolte RJM, *Macromolecules* **33**: 8289-8294 (2000).
- 96 Wang MJ, Wang H, Chen SC, Chen C and Liu Y, *Langmuir* **31**: 6971–80 (2015).
- 97 Jhaveri AM and Torchilin VP, *Front Pharmacol* **5**: 77 (2014).
- 98 Lazzari M and Torneiro M, *Polymers* **12**: 869 (2020).
- 99 Deng Z and Liu S, *Polymer* **207**: 122914 (2020).
- 100 Hasannia M, Aliabadi A, Abnous K, Taghdisi SM, Ramezani M and Alibolandi M, *J Controlled Release* **341**: 95–117 (2022).
- 101 Karayianni M and Pispas S, *J Polym Sci* **59**: 1874–1898 (2021).
- 102 Zhang X-Y and Zhang P-Y, *Curr Med Chem* **13**(2): 124 (2017).
- 103 Zhang L and Eisenberg A, *Science* **268**(5218): 1728 (1995).
- 104 Holder SJ, Hiorns RC, Sommerdijk NAJM, Williams SJ, Jones RG, Nolte RJM, *Chemical Communications* **14**: 1445-1446 (1998).
- 105 Rodrigues PR and Vieira RP, *European Polymer Journal*, **115**:45-58 (2023).
- 106 Moad G, Rizzardo E and Thang SH, *Chem Asian J* **8**: 1634-1644 (2013).
- 107 Moad G, *Polymer International* <https://doi.org/10.1002/pi.6424> (2023).
- 108 Bawa KK and Oh JK, *Mol Pharmaceutics* **14**: 2460 (2017).
- 109 Avramović N, Mandić B, Savić-Radojević A and Simić T, *Pharmaceutics* **12**: 298 (2020).
- 110 Hanafy NAN, El-Kemary M and Leporatti S, *Cancers* **10**: 238 (2018).
- 111 Jeong B, Bae YH, Lee DS and Kim SW *Nature* **388**: 860–862 (1997).
- 112 Perinelli DR, Cespi M, Bonacucina G and Palmieri GF, *J Pharma Investigation* **49**: 443 (2019).
- 113 Basu A, Kunduru KR, Doppalapudi S, Domb AJ and Khan W *Advanced Drug Delivery Reviews* **107**: 192–205 (2016).
- 114 Maeda T, *Bioengineering* **6**:107 (2019).
- 115 Meng X, Zhang X, Tong J, Sun H, Fawcett JP and Jingkai Gu, *Acta Pharmaceutica Sinica B* **11**(4): 1003e1009 (2021).

- 116 Tekale SU, Rottenberg Y, Ingle RD, Domb AJ and Pawar RP, *Polym Adv Technol* **32**: 3877 (2021).
- 117 Zhu Q, Zhang B, Wang Y, Liu X, Li W, *et al.*, *Polymers for Advanced Technologies*, **32**(3): 1262 (2021).
- 118 Hurst PJ, Rakowski AM and Patterson JP, *Nat Commun* **11**: 4690 (2020).
- 119 Lohmeijer BGG, Pratt RC, Leibfarth F, Logan JW, Long DA, Dove AP, Nederberg F, Choi J, Wade C, Waymouth RM and Hedrick JL, *Macromolecules* **39**(25): 8574 (2006).
- 120 Hurst PJ, Rakowski AM and Patterson JP, *Nat Commun* **11**: 4690 (2020).
- 121 Pooch F, Sliepan M, Svedstöm KJ, Korpi A, Winnik FM and Tenhu H, *Polym. Chem.*, **9**: 1848 (2018).
- 122 Caillol S, Lecommandoux S, Mingotaud AF, Schappacher M, Soum A, Bryson N and Meyrueix R, *Macromolecules* **36**: 1118 (2003).
- 123 Perin F, Motta A and Maniglio D, *Materials Science & Engineering C* **123**: 111952 (2021).
- 124 Feng H, Lu X, Wang W, Kang N-G and Mays JW, *Polymers* **9**: 494 (2017).
- 125 Gignes D and Trimaille T, *Advances in Colloid and Interface Science* **294**: 102483 (2021).
- 126 Cornel EJ, Jiang J, Chen S, Du J, *CCS Chem* **2**: 2104 (2020).
- 127 Jung J-J, Yu I, Nyamayaro K and Mehrkhodavandi P, *ACS Catal* **10**: 6488 (2020).
- 128 Zaky MS, Guichard G and Taton D, *Macromolecular Rapid Communications*, **43**(20): 2200395 (2022).
- 129 Oliveira ASR, Pereira P, Mendonça PV, Fonseca AC, Simões S, Serra AC and Coelho JFJ, *Polym Chem* **14**: 161 (2023).
- 130 Deokar MD, Garnaik B and Sivaram S, *ACS Omega* **7**: 9118 (2022).
- 131 Kontogiannis O, Selianitis D, Lagopati N, Pippa N, Pispas S, and Gazouli M, *Pharmaceutics* **15**: 501 (2023).
- 132 Vlachopoulos A, Karlioti G, Balla E, Daniilidis V, Kalamas T, Stefanidou M, Bikiaris ND, Christodoulou E, Koumentakou I, Karavas E and Bikiaris DN, *Pharmaceutics* **14**: 359 (2022).
- 133 Liu J, Xiao Y and Allen C, *J Pharm Sci* **23**:132-43 (2003).
- 134 Huynh L, Neale C, Pomès R and Allen C, *Nanomedicine: Nanotech, Biology and Medicine* **8**: 20 (2012).
- 135 Karplus M and McCammon JA, *Nat Struct Biol* **9**: 646 (2002).
- 136 Costache AD, Sheihet L, Zaveri K, Knight DD and Kohn J, *Mol Pharm* **6**:1620 (2009).
- 137 Shinoda W, DeVane R and Klein ML, *Current Opinion in Structural Biology* **22**:175–186 (2012).
- 138 Fedkin MV, Shin YK, Dasgupta N, Yeon J, Zhang W, van Duin D, van Duin K, Mori ACT, Fujiwara A, Machida M, Nakamura H and Okumura M, *J Phys Chem A* **123**: 2125 (2019).
- 139 Monti S, Jose J, Sahajan A, Kalarikkal N and Thomas S, *Phys Chem Chem Phys* **21**: 13099 (2019).
- 139 Kanjickal DG, Lopina ST, *Crit Rev Ther Drug Carrier Syst* **21**: 345 (2004).
- 140 (a) Grassi M and Grassi G, *Current Drug Del* **2**: 97 (2005); (b) Macha IJ, Ben-Nissan B, Vilchevskaya EN, Morozova AS, Emek Abali B, Müller WH, Rickert W, *Bioeng Biotechnol* **7**: 37 (2019).
- 141 Huynh L, Leroux JC and Allen C, *Org Biomol Chem* **7**: 3437-3446 (2009).
- 142 Souza ACS, *Appl Mater Interfaces* **12**: 5147–5156 (2020).
- 143 Le TC, Davis PJ and Uhlherr A, *J Chem Phys* **130**: 074901 (2009).
- 144 Xiang T-X and Anderson BD, *Adv Drug Del Rev* **58**:1357-1378 (2006).

- 145 Lipinski CA, Lombardo F, Dominy BW and Feeney PJ, *Adv Drug Deliv Rev* **46**: 3-26 (2006).
- 146 Jorgensen WL and Duffy EM, *Adv Drug Del Rev* **54**: 355-66 (2002).
- 147 Huynh L, Leroux JC and Allen C, *Org Biomol Chem* **7**: 3437-3446 (2009).
- 148 Costache AD, Sheihet L, Zaveri K, Knight DD and Kohn J, *Mol Pharm* **6**: 1620-1627 (2009).
- 149 Bégué D and Wentrup C, *J Org Chem* **79**: 1418 (2014).
- 150 Bunker A, *Physics Procedia* **34**: 24-33 (2012).
- 151 Tandon H, Chakraborty T, Suhag V, *Research Medical and Engin Sci* **7**(4):791 (2019).
- 152 Bégué D, Santos-Silva H, Dargelos A, Wentrup C, *J Phys Chem A* **121**: 8227 (2017).
- 153 Markovic M, Ben-Shabat S, Keinan S, Aponick A, Zimmermann EM and Dahan A, *Int J Mol Sci* **20**: 2210 (2019).
- 154 Kaviani M and Di Valentin C, *Nanoscale*, **11**: 15576-15588 (2019).
- 155 Chen X, Sun Z, Zhang H and Onsoni S, *Mol Phys* **118**(13): e1692150 (2020).
- 156 Sousa SF, Fernandes PA and Ramos MJ, *Phys Chem Chem Phys* **14**: 12431–12441 (2012).
- 157 Tomasi J, Mennucci B and Cammi R, *Chem Rev* **105**: 2999-3093 (2005).
- 158 Grimme S, Antony J, Ehrlich S and Krieg H, *J Chem Phys* **132**: 154104 (2010).
- 159 Grimme S, Ehrlich S and Goerigk L, *J Comput Chem* **32**: 1456-2465 (2011).
- 160 Car R and Parrinello M, *Phys Rev Lett* **55**: 2471–2474 (1985).
- 161 Warshel A, *Proc Natl Acad Sci USA* **75**: 5250–5254 (1978).
- 162 Aminpour M, Montemagno C and Tuszynski JA, *Molecules* **24**: 1693 (2019).
- 163 Siepmann J and Siepmann F, *Int J Pharma* **364**: 328 (2008).