Synthesis and spectroscopic signatures of a novelpolylactide-based nano-organogel

Frank O. Ohwoavworhua[1,2]✉, James W. Mitchell[2]

[1]Department of Pharmaceutical Sciences, College of Pharmacy, Howard University, Washington DC, USA
[2]Department of Chemical and Biomolecular Engineering, College of Engineering and Architecture, Howard University, Washington DC, USA

✉**Correspondence to:**
Frank O. Ohwoavworhua
Department of Pharmaceutical Sciences, College of Pharmacy, Howard University, Washington DC, USA
Department of Chemical and Biomolecular Engineering, College of Engineering and Architecture, Howard University, Washington DC, USA
Email: frankohwo@yahoo.com

Article History
Received: 04 August 2020
Accepted: 11 September 2020
Published: September 2020

Citation
Frank O. Ohwoavworhua, James W. Mitchell. Synthesis and spectroscopic signatures of a novelpolylactide-based nano-organogel. *Drug Discovery*, 2020, 14(34), 296-306

Publication License

ISSN 2278–540X; EISSN 2278–5396

General Note

ABSTRACT

The low molecular weight gelators (LMWGs) are small organic molecules known for their gel forming abilities. Depending on experimental conditions, these molecules self-assemble and immobilize organic solvents or water to form organogels or hydrogels, respectively. They find applications in a variety of fields including material science, environmental science and drug delivery. This paper reports a serendipitous observation of the gelation of polylactide (PLA) derivative in a nonpolar solvent to form a new nano-organogel. The structural characteristics of the gel were evaluated. The results show nanometer-sized hexagonal particles, average molecular weight of <1000, presence of double bonds and carboxylic acid functional groups, and nonionic amphiphilic-like structure, which are inherent features that would make the nanostructure a potential versatile drug carrier. Additionally, the abundance of lactyl ($CH3CHCO.O$) repeating units in its chain length that are contributory to its hydrophobicity suggestsits capability to load poorly water-soluble drugs. Also, the chemistry of the nano-organogel formation is presented. Thus, a new facile method of obtaining low molecular weight, bi-functionalizednano-organogel, with high potential of loading bioactive agents, as well as functioning as excellent adsorbent for organic liquid pollutants, has been developed.

Keywords: Organogelators, nano-organogel, supramolecular-gel, polylactide, drugs delivery.

1. INTRODUCTION

Poly (lactic acid) (PLA), polyester, is a biodegradable polymer approved for human use by the Food and Drug Administration (FDA). Like other polyesters, PLA is biocompatible, non-immunogenic and non-toxic. These attributes have made it and its copolymers popular in drug delivery.[1-3] In fact, PLA and its derivatives, including poly (lactide) -co- (glycolide) (PLGA), poly (lactide) -co- (2, hydroxyethyl methacrylate) (PLA-co-HEMA), poly (ethylene glycol)-polylactide (PEG-co-PLA), poly (lactic acid-co-glycidyl methacrylate) P(LLA-co-GMA) etc., are widely used for controlled delivery of drugs, orthopedic implants, surgical sutures, staples, and scaffolds for cell engineering.[1,2,4,5] PLA is synthesized by the two main methods, namely: by polycondensation of lactic acids and by ring-opening polymerization (ROP) of lactides, i.e cyclic diesters of various isomeric forms – L, D and DL (or *meso*form).[6] However, to optimize the use of PLA in drug delivery, its two major limitations, namely: hydrophobicity (due to thecrystallinity) and lack of reactive functional group must be addressed.[1,6,7] The hydrophobic characteristic of the PLA makes it not only difficulty to be dispersed in water, but also rendered the nanoparticles made purely from PLA easily opsonized by mononuclear phagocyte system (MPS) – hence the nanoparticles are rapidly cleared out from the blood circulation. One way this drawback has been handled involved the introduction of hydrophilic blocks, such as polyzwitterions and poly ethylene glycol (PEG) into PLA, thereby resulting in amphiphilic PLA-containing polymer.[2,6] The amphiphilic characteristics of the PLA-based copolymers make them to self-assemble into micelles in aqueous solvents to form nanoparticles with both hydrophobic core and hydrophilic corona. The hydrophobic core then acts as reservoir for hydrophobic drugs, while the hydrophilic coronas ensure the water-solubility, as well as prevent protein adsorption, and hence make the micelles to circulate for a longer time in the blood.[2,8]

The lack of reactive functional groups makes the use of PLA in free-radical polymerization reaction for synthesis of nanoparticles none feasible. This limitation makes the fabrication of nanoparticles with PLA to be restricted to the use of preformed polymers.[3] Also, the lack of reactive functional groups not only made it difficult to covalently attach targeting moieties to the surface of its nanoparticles, but also hampered cross-linked networks.[3] It should be noted that the cross-linked network would function to control drug release and degradation rate, that is improve stability.[2,7,9,10] In order to circumvent the lack of reactive groups, researchers investigated copolymers of PLA-co-HEMA and other PLA-derivatives – as such systems hold the promise of providing novel biodegradable, functionalized polymers with tunable characteristics, as well as allow cross-linked networks.[2,7,9,10] Thus, the foregoing viewpoints provide the rationale, in part, for this work. It should be added that the PLA-co-HEMA in previous investigation wasused as a macromonomer in a dispersion polymerization reaction, which involves multi-steps and reagents/solvents, to generate monodispersed functionalized nanoparticles.[7]

The low molecular weight gelators (LMWGs) are small organic molecules known for gel forming abilities.[11-16] These molecules, depending on experimental conditions, do self-assemble and immobilized organic solvents or water to form oranogels or hydrogels, respectively. In recent years, there has been increasing interest in the research, particularly as they are being reputed to find applications in a variety of fields including material science, cosmetics, biomedicine, drug delivery, environmental sciences etc.[13-15] The supramolecular structures formed due to self-assembling of these molecules are believed to result through secondary interactions like H-bonding, π-stacking, metal coordination, donor-acceptor interaction, hydrophobic forces, electrostatic, or van der Waals' interaction.[13-18] Because these functional gels are formed predominantly by non-covalent interactions, they are able to transform from gel-sol in response to appropriate external stimuli, which may include UV-vis light, shear forces, magnet field, electric fields, heat, pH changes, oxidation-reduction etc.[13,14]

While several gels have been developed with well define structure-property correlation by employing advanced synthetic methodologies, [13,14] it is a common knowledge among researchers in this field that their first discoveries are usually by serendipity. This paper reports another example of laboratory pleasant surprises – a spontaneous formation of organogel in the experimental flask. Wedetails a comprehensive spectroscopic studies, structure, as well as proposed the chemistry for the formation of the nano-organogel.

2. MATERIALS AND METHODS

Materials

L-lactide (Polyscience Inc.) was recrystallized twice with toluene before use. Toluene (Acros, 99%) was purified by drying over CaH_2 to remove moisture and oxygen and distilled under reduced nitrogen atmosphere. Hydroxyethyl methacrylate (HEMA) (Aldrich, 97%) was dried over molecular sieves (4 A°) for 24 hours and distilled under negative pressure before use. Stannous octoacte (Sigma, 95%) and phosphorous pentaoxide (Aldrich, 97%) were used as received. All other reagents were of analytical grade and used without further purification.

Synthesis of a new nano-organogel

A low molecular weight and carboxylic acid group functionalized organogelatorwas prepared directly from the monomer of L-lactide and HEMA (as initiator) by novel ring-opening-dispersion polymerization. The reaction was carried out in the presence of 4-tert-butylcatechol (TBC), and stannous octoate, as a catalyst, using a published method,[7,19] with slight modifications. Briefly, L-lactide (6.0234 g, 0.0418 mole), HEMA (5.0689 mL, 0.0418 mole), 4-tert-butylcatechol (347.32 mg) and drops of stannous octoate were placed in a 100 mL round-bottom flask equipped with a magnetic stirring bar. The reaction flask was kept under vacuum for 10 minutes and polymerization was carried out in an inert atmosphere by flushing the flask with nitrogen gas for 24 hours within a silicone oil bath kept at 98 -102^{o}C. After polymerization was completed, the product (nano-organogel of PLA-HEMA i.e. co-polymeric nanogel) was purified.

Purification of nano-organogel

The synthesized nano-organogel was purified and freed from unreacted immobilized HEMA, and tertbutyl catechol, by rinsing in water thrice, followed by stirring the nano-organogel in excess water overnight (since these reagents are miscible/soluble in water). The copolymericnano-organogel were collected by filtration and dried at room temperature in a vacuum desiccator under reduced pressure over phosphorous pentaoxide for 72 hours.

Characterizations of the nano-organogel

Scanning Electron Microscopy

Dilute suspensions of the nanoparticles in 0.1 N hydrochloric acid and Tetrahydrofuran (THF) were placed on a carbon tape affixed to a specimen steel stub (SPI Supplies, Inc) and dried for 24 hours in a vacuum oven. The samples were coated with gold for 2 minutes under argon atmosphere using a Hummer sputtering machine. The samples were then viewed under high vacuum at 10 kV and images taken at different magnifications using a scanning electron microscope.

Fourier-transformed infrared (FT-IR) spectroscopy

A 2.0 mg nano-organogel sample was placed in the sample port holder and the sample was characterized using FTIR spectrometer. The sample was scanned 64 times at a resolution of 4 cm^{-1} from 4000 and 650 cm^{-1}. This determination was carried out using a Perkin Elmer Spectrum 100 FR-IR spectrometer.

Proton nuclear magnetic resonance (NMR) spectroscopy

A 2 mg LMWG sample was added to 5 mL of $CDCl_3$ in a glass vial, followed by thorough vortexing. The mixture was sonicated at 60 °C for 30 min, and subsequently filtered to remove un-dissolved material. A 0.5 mL of the resulting clear solution was transferred to a 5 mm NMR tube. A proton NMR spectrum was recorded using residual proton resonance of the solvent as the internal standard. This determination was carried using the Bruker AVANCE 400 MHz NMR spectrometer.

Energy dispersive X-ray spectroscopy (EDS)

Energy dispersive X-ray analysis was used to identify the elemental composition of the nano-organogel. EDS measurements were performed on a Compact Detector Unit (CDU) (EDAX, Mahwah, NJ, USA) incorporated into a JEOL JSM – 7600 F field emission scanning electron microscope. A 2 mg sample of the LMWG was suspended in water and then sonicated at 35 °C for 30 minutes. The particle suspension was further diluted 100-fold in water and a drop of the 10 μL diluted solution was placed on a carbon stub and air-dried. The EDS spectrum was obtained at an acceleration voltage of 20 kV and collected for 20 s. Mapping was collected using pseudo-colors to represent two-dimensional spatial distribution of energy emissions of chemical elements present in the sample.

Matrix-assisted laser desorption Ionization time-of-flight mass spectroscopy (MALDI- TOF MS)

MALDI-TOF MS measurements were performed on a Voyager DE-STR instrument (Applied Biosystems) equipped with a pulsed nitrogen laser (20 Hz, 337 nm). The conditions: acceleration voltage 20 kV, grid voltage 64% (reflectron) and delay time 350 ns were used. The spectrum was recorded in the reflectron mode with DHB (dihydrobenzoic acid) as matrix. A total of 300 laser shots were summed for each spectrum.

For the measurements on the Voyager DE-STR, 10 μL of sample (1mg/mL in DCM) was mixed with 30 μL of DHB (10 mg/mL in methanol) matrix solution and vortex for 60 s. The resulting solution was then spiked (1 μL) on a stainless steel Bruker Anchor 100 sample plate. The preparation was allowed to dry at room temperature and subjected to MS.

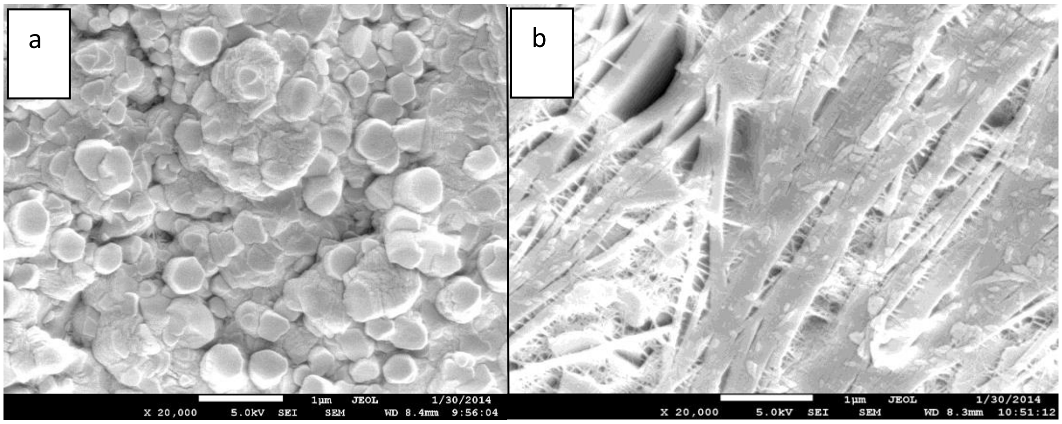
3. RESULTS AND DISCUSSION

Synthesis of the nano-organogel

The synthesis of the nano-organogel is facile, occurs in one-vessel and is surfactant-free. The reacting species including the catalyst, HEMA, stannous octoate, are FDA approved.[19,20] Also, the average percentage yield of nano-organogel from separate syntheses conducted under identical conditions was 82.6 ± 1.4, (n = 3). The synthesis involves ring-opening polymerization of the monomer lactide, and the formation of discrete monodispersed nanometer size particles, a process that occurs during dispersion polymerization, and all in one vessel, we have coined ring-opening-dispersion-polymerization reaction to describe this novel method.

Characterization of the nano-organogel

Figure 1 represents the SEM micrograph of the nano-organogel. Panel A and B showed micrographs of the nano-organogel mounted from 0.1 N hydrochloric acid, and THF, respectively. In panel A the hexagonal shaped discretenanomeric-size (average 307 nm) particles are revealed, while panel B reveals the lamellar-like and network nature. Tetrahydrofuran is a water-miscible organic liquid. It is a moderately polar solvent that dissolves a wide range of non-polar and polar chemical compounds.[21]Thus, the THF treated nanogel showed highly porous fiber network with channels of nanometer dimensions. Van-Esch and Feringa reported similar observation and explained that removal of solvent from organogel systems results in a network structure with highly porous self-supporting monolithic foams.[22]



Size in μm

Figure 1. Scanning electron microscopy micrograph of nano-organogel; a) dispersed in 0.1 N HCl, b) dispersed in dilute THF, original magnification 20,000X

Figure 2 represents the FT-IR spectrum of the nano-organogel. Characteristic peaks of interest include bands at 3486-, 2990- and 1726 cm^{-1}, which are due to the hydroxyl group, C-H stretching, and an acid carbonyl group, respectively. The rudimentary peak which appears at 1640 cm^{-1} (almost at the base of the prominent acid carbonyl band) is very significant, and corresponds to C=C vibrations. Its presence shows the vinyl unsaturation of the hydroxyethyl methacrylate and confirms its conjugation or its incorporation into the poly lactide chain. The assignments of these characteristics bands are in accordance with the literature.[19,23]

The characteristic peaks underscore unequivocally that the co-polymeric nano-organogel is hetero-bifunctionalized with double bonds (alkene) and carboxylic acid groups. The significance of this is that the nano-organogels have outer shells that are hydrophilic in nature. The hydrophilic outer layer facilitates nanocarriers to evade being captured by the reticuloendothelial system (RES).[2] As a result, these nanoparticles, with their loaded drugs, have potentials to have a prolonged half-life of circulation in the bloodstream. This will in turn impact on their effective drug delivery ability. Additionally, the core-shell structure will allow the co-polymeric nano-organogels to maintain their water solubility by inhibiting the aggregation of the hydrophobic cores due to the presence of the hydrophilic shell.[2,24]

Analysis of the proton NMR spectrum (Figure 3) shows the presence of a C=C bond with olefinic protons at about δ = 5.57 ppm and δ = 6.19 ppm. Huang and Onyari reported that these chemical shifts confirm the incorporation of HEMA into the polylactic acid chain, and as a unit forms the nano-organogel system.[19] Also, clearly observed is one sharp multiplet center at δ = 4.35, which corresponds to the four hydrogens of the oxyethylene residue. In addition, the signal at δ = 1.95 corresponds to α-CH$_3$ proton of the methacrylic HEMA residue. These data are consistent with previous reports on the synthesis of the PLA-HEMA copolymer.[25]

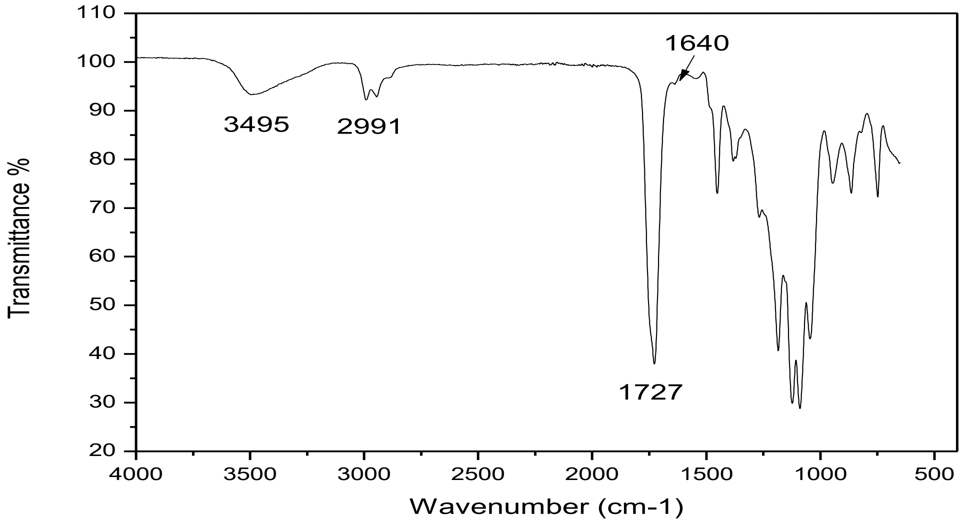


Figure 2 FT-IR spectrum of the copolymericnano-organogel, representing the characteristic functional groups of the gel.

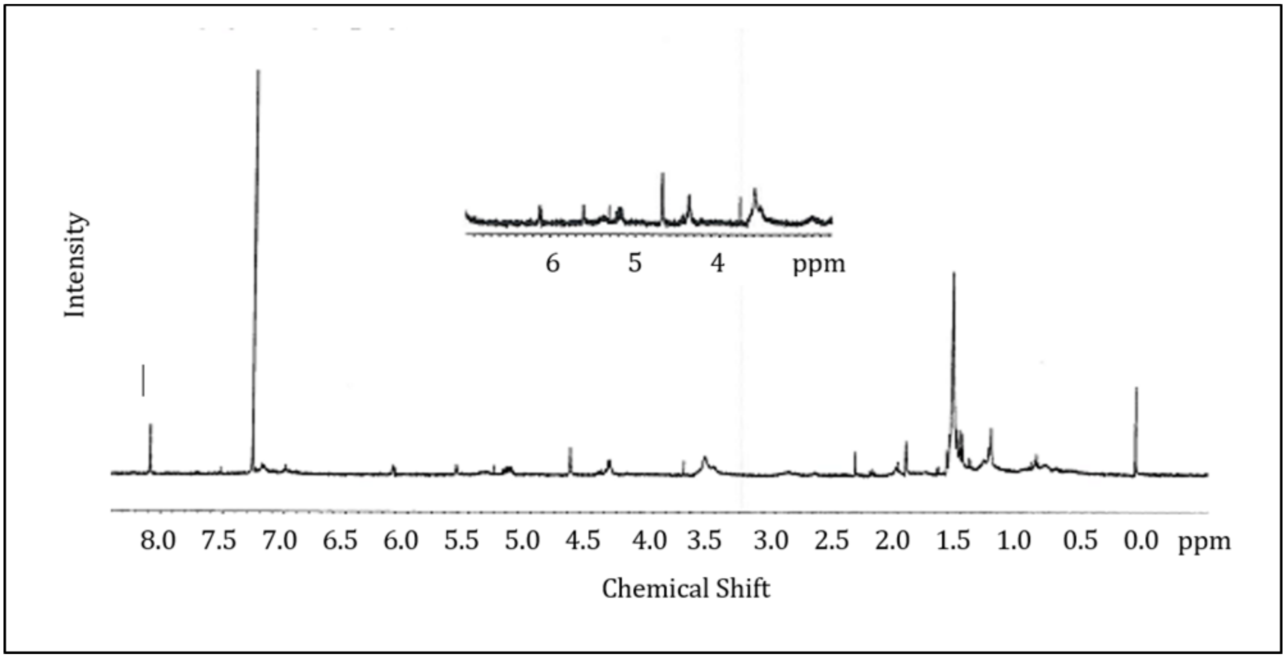


Figure 3 Proton NMR spectrum of the copolymericnanoorganogel in deuterated chloroform ($CDCl_3$), representing the copolymeric characteristic of the gel.

The mass spectrum of the copolymericnano-organogel is shown in Figure 4. A unimodal peak distribution can be observed with a maximum at m/z ca 1017. Also, it can be seen that a series of main peaks are separated by an interval attributing to lactyl unit, $CH_3CHO.CO$, (72 mass units, which is derived from lactic acid after the loss of water during polymerization). The maximum value represents the Na+ cationized PLA-HEMA co-oligomer (i.e. M + Na). The ion mass is corrected for the mass of the cation, subtracting 23 in this case for Na+ cationization.[26,27] After the sodium ion is accounted for, the average molecular weight becomes 994. It should be noted that polymers do not have exact molecular weight and display a distribution of molecular weights.[28] In the determination of molecular weights of polymers/oligomers, a range of analytical techniques is available including GPC, osmometry, light scattering, and mass spectrometry. Though these traditional and non-traditional methods have different limitations in providing accurate mass number and molecular weight data, they are nonetheless widely used in polymer characterizations, especially in application areas, where only a general assessment of the molecular weight is required.[27] The MALDI-MS is reputed to provide a more accurate molecular weight result than those obtained from the methods above. Its utility in analysis of molecular weight of polymeric systems has been demonstrated.[27] Two features of MALDI that contributes to its popularity in polymer molecular weight analysis are: (1) analyte polarity is not critical and (2) MALDI generates almost exclusively singly charged ion with most matrices. Hence, in principle, MALDI mass spectra are interpretable even if a polymer sample consists of a large number of oligomers with different masses due to their chain lengths.[29]

Figure 5 shows the EDS spectrum of the nano-organogel system. Qualitatively, the characteristic peaks of carbon and oxygen were detected. The absence of peak for elemental tin clearly indicates that the stannous octoate, which functions as a catalyst in the synthetic reaction, was not incorporated in the synthesized copolymer that formed the nanoparticle system. The quantitative information was obtained by comparing the areas of the peaks in the spectra with the area of single element standard peaks; the ratio obtained was corrected with the standard ZAF computer program.[30] The error inherent in this type of analysis is generally less than 5%. This measurement showed that the nanoparticle system is composed of carbon 55.3% and oxygen 44.7% by weight. The energy dispersive x-ray analysis EDX is used to analyze the elemental composition of materials (with atomic number above 4 (Be) to 92 (U)). The detectable atomic number range explains why hydrogen composition of nanomaterials cannot be quantified by this method. This technique provides both qualitative and quantitative information.[30]

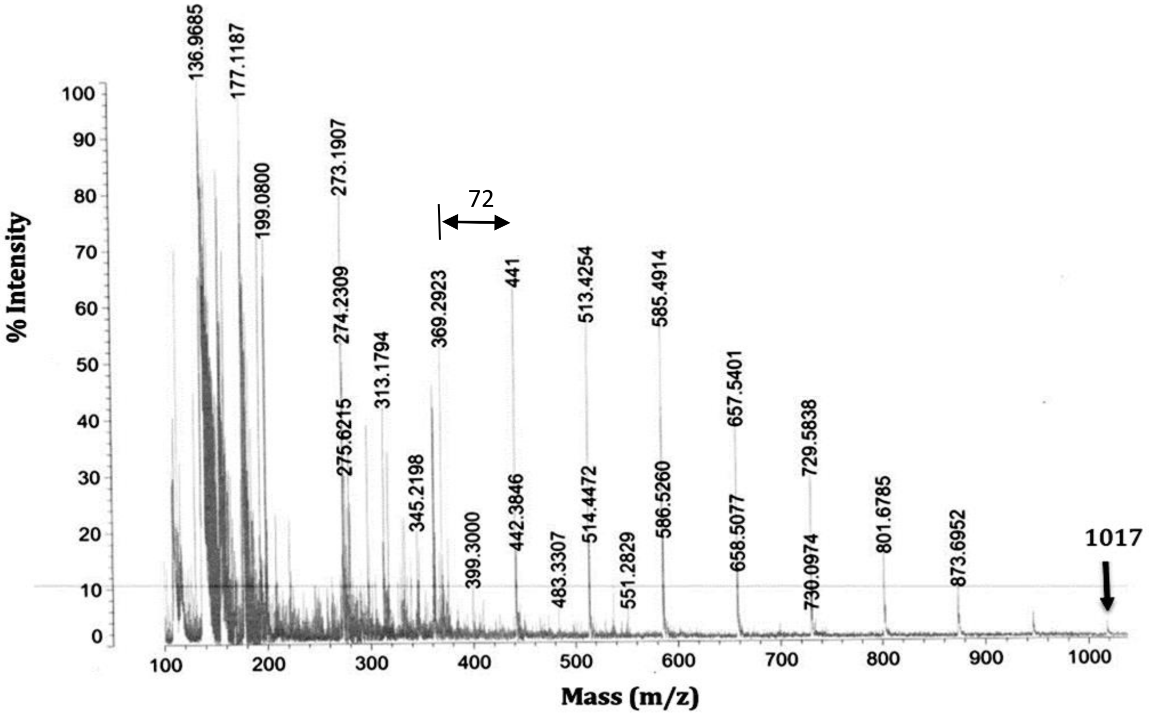


Figure 4.MALDI-MS spectrum of the copolymericnano-organogel, representing the average molecular mass of the gel.

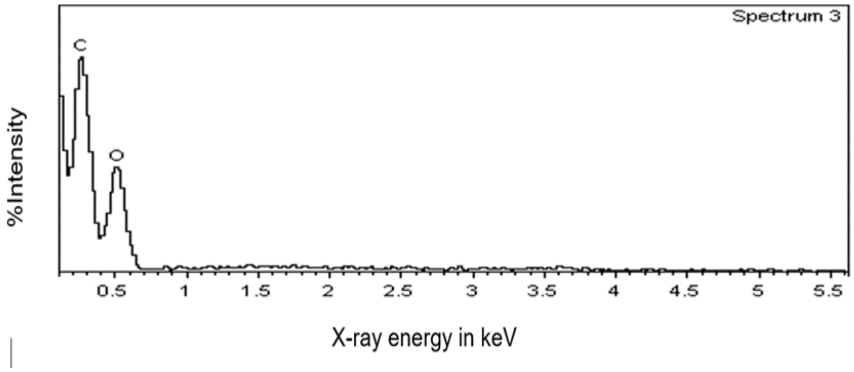


Figure 5. EDS spectrum of the copolymeric nano-organogel, demonstrating the elemental composition of the gel.

The structure of the molecular gelator that formed the nano-organogel

The polymerization reaction between the monomers, L-lactide, and 2, hydroxyethyl methacrylate (HEMA), in the presence of tin (II) octoate, as a catalyst, is illustrated in Equation 1. Tertbutyl catechol is the inhibitor, and the reaction temperature was 100 °C. The reaction product in Eq. 1 self-assembles in the excess solvent, HEMA, to form the nano-organogel. The chemical structure reveals inherent features with useful implications for drug delivery, namely:

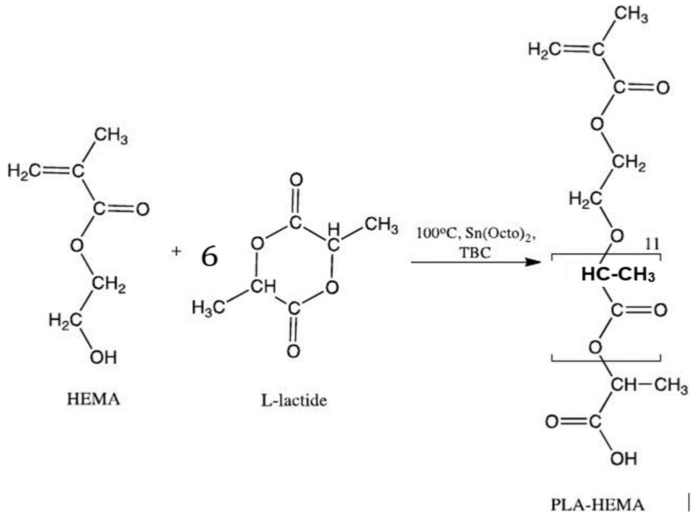
i. The presence of lactyl repeating units, which is somewhat akin to polyoxylpropylene unit, also known as PPO units. This unit being in abundance in the chain length confered on the nano-organogelthe hydrophobicity. This explains why the excess organic solvent HEMA was immobilized to form the gel. This ability is indicative ofa high capacity to load poorly water-soluble cancer drugs.

ii. The nonionic surfactant-like structure would not only facilitates membrane fluidity, but also serves as effective inhibitor of P-glycoprotein (permeability glycoprotein, abbreviated P-gp or Pgp), which is multi-drug resistance protein responsible for efflux of drugs across cell membranes.[31,32]P-gp is expressed extensively in the GIT and reputedly contributes to reduced oral absorption of drugs, resulting in reduced efficacy of some drugs that are said to be P-gp substrates. It is also widely distributed and expressed in the liver cells, in the cells of the proximal tubule of the kidney and the capillary endothelial cells of the blood-brain barrier. Additionally, some cancer cells express large amount of P-gp and is known to contribute to the multi-drug resistance exhibited by most cancer cells.[33]Other chemically similar molecules, such as Tween 80, Cremophore EL and Pluronic, which have nonionic characteristics, as well as having, repeating polyethylene (PEO) units, have shown inhibitions for P-gp to increase the concentrations of poorly water-soluble drugs across biological membranes.[31]

iii. The medium chain length, coupled with the carboxylic group terminal should make the nano-organogel a candidate for monocarboxylic acid (MCT) transporters, which are one of the main transporter systems in the intestine and kidney, as well as being overexpressed in most cancer cells.[31-33] The MCTs are involved in the transport of fatty acids, and monocarboxylates, such as lactate, pyruvate and ketone bodies across plasma membrane and mitochondrial inner membrane.[32]

iv. The average molecular weight of the nanomaterial is low (average M. W ≤ 1,000), which is quite unique for the fabrication of polymeric nanomaterials for drug delivery. This feature is consistent with increased permeability across cell membranes, and hencewill facilitate increased bioavailability of drugs loaded in it.

v. The functional carboxylic end group of the nano-organogel system will make it capable of being modified by secondary chemical reactions --- making it feasible for conjugation of oligonucleotides, imaging contrasting agents, targeting moieties etc.



.. Eq. 1.

Explanation of the chemistry and proposed synthetic route for the nano-organogel formation

The Tin (II) octoate, a covalent metal carboxylate, is considered the most frequently used catalyst for polymerization of cyclic esters.[34-41] The extensive investigations of the tin (II) octoate catalyzed lactide ring-opening polymerization have resulted in two main proposed mechanisms for this reaction. First of these mechanisms, is the direct catalytic action of tin (II) octoate.[38,39,41] It involves the activation of the monomer, L-lactide, by tin (II) octoate to result in a donor-acceptor complex, which in turn participates directly in the propagation step for the reaction. The product of the reaction involving this mechanism does not incorporate the Sn (II) atom within the polymer at any stage of the polymerization.

The second mechanism, which is known as an insertion coordination step, involves Sn $(Oct)_2$ reacting with the HEMA (a hydroxyl group bearing reagent) to form an intermediate, which is tin (II) alkoxide or hydroxide.[36,37,41] In this mechanism, it is believed that the polyester chain growth proceeds via monomer insertion at the metal alkoxide active center. A previous investigator indicated that in this mechanism, Sn (II)-containing species are incorporated at the end groups in one of the propagating macromolecules.[37] It is significant to note that a common point of agreement in both mechanisms is the view that hydroxyl groups initiate the lactone and/or cyclic di-ester (lactide) polymerization.[38]

In contrast to the proposed insertion coordination step, findings from the characterization of our copolymericnano-organogel gave definite clues that support the first mechanism. The EDS spectrum showed that the Sn (II) atom was not incorporated into the nanoparticle. Hence, on this basis, it is concluded that the formation of the copolymeric nanoparticles proceeded via the first mechanism – i.e. by the direct catalytic action of $Sn(Oct)_2$, which forms a donor-acceptor complex. Secondly, the FT-IR spectrum of the nano-organogel (see Figure 2) shows prominent absorption bands at 1726- and 3486- cm^{-1}, which indicate carbonyl- and hydroxyl groups that are characteristic of an organic acid. The –COOH group has resulted from the breaking of alkyl oxygen bonds of L-lactide. The L-lactide in the ring opening polymerization reaction does proceed either by breaking of acyl oxygen bonds or by alkyl oxygen bonds.[25,42] However, the breaking of alkyl oxygen bonds involves higher activation energy.

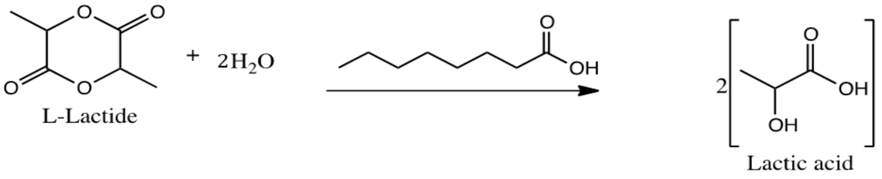
Lastly, another important clue that contributes to the elucidation of the mechanism is the information provided by MALDI-MS determination of thecopolymericnano-organogel. This determination indicates that it is composed of low molecular weight material. Hence, a sudden chain growth or propagation step did not occur. This is plausible since the excess HEMA in the reaction would have inhibited the propagation step.

All things taken together, the overall reaction pathway would include the following important steps:

The stannous octoate catalyzed ring-opening polymerization reaction proceeds via an intermediate (alkoxide) with octanoic acid generated as shown in Equation 2.

Sn(Oct)2 + R—OH ↔ R—O—Sn—Oct + Oct—H ...Eq. 2.

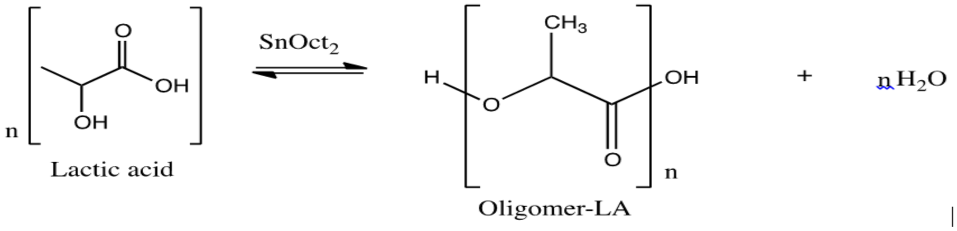
Where R-OH represents HEMA, and Oct-H represents Octanoic acid



..........Eq. 3.

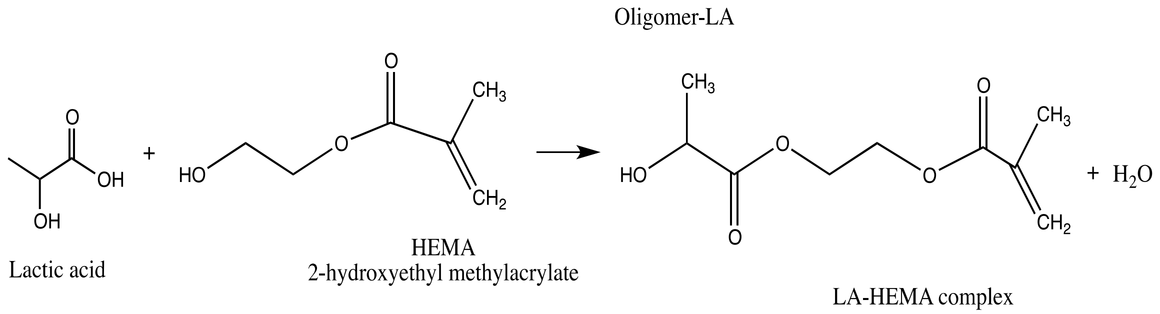
Additionally, in the presence of octanoic acid, which may also occur at trace levels together with water in stannous octoate, the L-lactide is hydrolyzed to form lactic acid as shown in Equation 3.[39]

The lactic acid in the presence of the catalyst could have polymerized to form an oligomer of lactic acid (Oligo (L-lactic acid)), as shown in Equation 4. In the presence of excess HEMA this propagation step is restricted.



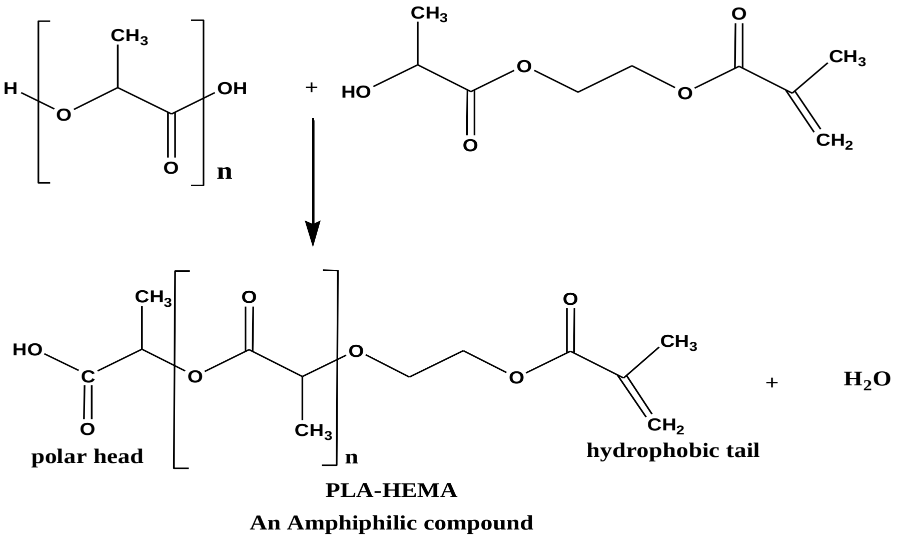
...Eq. 4

Another reaction that could have occurred might involves lactic acid and HEMA to generate the LA-HEMA complex, as shown in Equation 5.



Eq. 5.

Finally, the oligo-L-lactic acid then reacts with the LA-HEMA complex to form a final product,nano-organogel - a PLA-HEMA amphiphile. The unreacted (excess) HEMA, acting as a non-solvent for the amphiphile, makes it self-assemble as nano-aggregates that result in formation of low molecular weight nano-organogel as shown in Equation 6.



……. Eq. 6.

4. CONCLUSION

PLA-based nano-organogel has been successfully synthesized via a novel ring-opening-dispersion polymerization reaction, which occurred in one vessel and is surfactant-free. The supramolecular gel shows distinct characteristics features of hexagonal shaped nanometer particles and a highly porous network-like lamellar structure. Other features of the gel include average low molecular weight of <1000, bi-functionalized at the terminals with C=C and COOH groups and its nonionic amphiphilic properties, with PPO-like repeating unit in its chain. These features suggest that the nano-organogel would be a potential versatile nanocarrier for poorly water-soluble drugs. Thus, this work provides a novel facile method for developing functionalized and low molecular weight nanocarrier.

Author Contributions

Frank Ohwoavworhua carried out the experimental synthesis and characterizations, as well as wrote the main manuscript. James W. Mitchell supervised the work. Both authors reviewed the manuscript.

Peer-review

External peer-review was done through double-blind method.

Funding

This study has not received any external funding.

Conflict of Interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

REFERENCES & NOTES

1. Wang, J., Li, S., Han, Y., Guan, J., Chung, S., Wang, C. & Li, D. Poly (ethylene glycol)-polylactidemicells for cancer therapy. *Frontiers Pharmacol.* 9, 202 (2018).
2. Feng, C., Piao, M. & Li, D. Stereocomplex-reinforced pegylatedpolylactide micelle for optimized drug delivery. *Polymers*8, 165 (2016).
3. Adesina, S. K., Holly, A., Kramer-Marek, G., Capala, J. &Akala, O. E. Polylactide-based paclitaxel-loaded nanoparticles fabricated by dispersion polymerization: characterization, evaluation in cancer cell lines, and preliminary biodistribution studies. *J. Pharm. Sci.* DOI 10.1002/JPS.24061 (2014).
4. Petchsuk, A., Submark, W. & Opaprakasit, P. Development of crossliknablepoly(lactic acid-co-glycidyl methacrylate) copolymers and their curing behaviors. *Polymer J*. 45, 406-412 (2013).
5. Czelusniak, I., Khosravi, E., Kenwright, A. M. & Ansell-Christopher W. G. Synthesis, characterization and hydrolytic degradation of polylactide-functionalized polyoxanorbornenes. *Macromolecules*40, 1444-1452 (2007).
6. Oh, J. K. Polylactide (PLA)-based amphiphilic block copolymers: synthesis, self-assembly and biomedical applications. *Soft Matter* 7, 5096-5108 (2011).
7. Adesina, S. K. & Akala E. O. Biodegradable stealth polymeric particles fabricated using the macromonomer approach by free radical dispersion polymerization. *US Patent* 2012/0129797 A1 (2012).
8. Wang, J., Shen, K., Xu, W., Ding, J., Wang, C. & Chen, X. Stereocomplex micelle from nonlinear enantiomeric copolymers efficiently transports antineoplastic drug. Nanoscale*Res. Lett.*10, 206 (2015).
9. Samarajeewa S, Shrestha R, Elsabahy M, Karwa A, Li A, Zentay RP, Kostelc JG, Dorshow RB, Wookey KL. In vitro efficacy of paclitaxel-loaded dual responsive shell cross-linked polymer nanoparticles having orthogonally degradable disulfide cross-linked corona and polyester core domains. *Mol. Pharm.*10, 1092-1099 (2013).
10. Ding, J. Z., Zhuang, X., Xiao, C., Cheng, Y., Zhao, L., He, C., Tang, Z. & Chen, X. Preparation of photo-cross-linked pH-reponsive polypeptide nanogels as potential carriers for controlled drug delivery. *J. Mater. Chem*. 21, 11383-11391 (2011).
11. Wang, Y., Lovrak, M., Liu, Q., Maity, C., LeSage V. A. A., Guo, X., Eelkema, R. & van Esch, J. H. Hierarchically compartmentalized supramolecular gels through multilevel self-sorting. *JACS*141, (7) 2847-2851 (2018).
12. Basu, N., Chakraborty, A. &Ghosh, R. Carbohydrate derived organogelators and the corresponding functional gels developed in recent time. *Gel* 4,(2), 52 (2018).
13. Wangkhem, P. S. & Rajkumar, S. S. A new class of organogelators based on triphenylmethyl derivatives of primary alcohols: hydrophobic interactions alone can mediate gelation. *Beilstein J. Organic Chem.*13, 138-149 (2017).
14. Nikiforidis, C. V.& Scholten, E. Self-assemblies of lecithin and alpha tocopherol as gelators of liquid materials *RSC Adv.*4, 2466-2473 (2014).
15. Ajayaghosh, A. & Praveen, V. K. π – Organogels of self-assembled p – phenylenevinylenes: soft materials with distinct size, shape and functions. *Acc. Chem. Res.*40, 644-656 (2007).
16. George, M. & Weiss, R. G. Molecular organogels. Soft matter comprised of low molecular mass organic gelators and organic liquids. *Acc. Chem. Res.*39, 489-497 (2006).
17. Debnath, S. et al. Tunable supramolecular gels by varying thermal history. *Chemistry: A Europ. J.*doi: 10. 1002/chem.201806281(2019).
18. Weiss, R. G. Controlling variables in molecular gel science: how can we improve the state of the art? *Gel* 4(2), 25 (2018).
19. Huang, S. &Onyari, J. M. Multicomponent polymers poly (lactic acid) macromonomers with methacrylate terminal and copolymers of poly (2-hydroxyethyl methacrylate). *JMS Pure Appl. Chem. A*33, 571-584 (1996).
20. Gerhardt WW, Noga DE, Hardcastle KI, Garcia AJ, David M, Collard WM. Functional lactide monomers: methodology and polymerization. *Biomacromolecules* 7, 1735 -1742 (2006).
21. Pruckmayr, G., Dreyfuss, P. & Dreyfuss, M. P. Polyethers, tetrahydrofuran and oxetane polymers, In: Kirk-Othmer*Encyclopedia of Chemical Technology*. John Wiley & Son, Inc. (1996).
22. vanEsch JH; Feringa BL. 2000. New functional materials based on self-assembling Organogels: From Serendipity towards Design. *Angew. Chem. Int. Ed.* 2000, *39*, 2263–2266.
23. Pavia, L. D., Lampman, M. G., Kriz, S. G. & Vyvyan, A. J. *Introduction to Spectroscopy*, 5^{TH} ed. CA, Belmont: Cengage Learning. 15-125p (2013).
24. Yokoyama, M. Novel passive targetable drug delivery with polymeric micelles. In: Okano T (ed), *Biorelated Polymers and*

Gels: Controlled Release and Application in Biomedical Engineering. UK, London: Academic Press (1998).

25. Eguiburu, J. L., Fernandez-Berridi, M. J., Cossio, F. P. & San Roman, J. Ring-opening polymerization of L-lactide initiated by (2-Mathacryloxy) ethyloxy-aluminiumtrialkoxides. 1. Kinetics. *Macromolecules*32, 8 252-8258 (1999).
26. Payne, M. E. & Grayson, S. M. Characterization of synthetic polymers via matrix assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry. *J. Vis. Exp.*136, e57174, doi: 10.3791/57714 (2018).
27. Zhu H, Yalcin T, Li L. Analysis of the accuracy of determining average molecular weights of narrow polydispersity polymers by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. *J. Am. Soc. Mass Spectrom.*9, 275-281 (1998).
28. Odian, G. *Principles of Polymerization*. 4thEdition. NY: Wiley-Interscience (2004).
29. Dey, M.Castoro, A. J. Wilkins, C. L. Determination of molecular-weight distributions of polymer by MALDI-ToF MS. *Analytical Chem.*67,1575-1579 (1995).
30. Goldstein, J., Newbury, D. E., Joy, D. C., Lyman, C. E., Echlin, P., Lifshin, E., Sawyer, L. C. & Michael, J. R. *Scanning Electron Microscopy and X-Ray Microanalysis*. 3rded. New York: Springer. 1-50p (2003).
31. Rege, B. D., Kao, J. P. &Polli, J. E. Effects of nonionic surfactants on membrane transporters in Caco-2 cell monolayers. Eur J Pharm Sci 16, 237-246 (2002).
32. Halestrap, A. P. Monocarboxylic acids transport. *Compr. Physiol.* 3(4), 1611 -1643 (2013).
33. Washington, N., Washington, C. & Wilson,C. *Physiological Pharmaceutics: Barriers to Drug Absorption*, 2nd Edition, Taylor and Francis Inc. (2000).
34. Lee, C. & Hong, S. An overview of the synthesis and synthetic mechanism of poly (lactic acid). *Mod. Chem. Appl.* 2(4), 1-5 (2014).
35. Maharana, T., Mohanty, B. & Negi, Y. S. Melt-solid polycondensation of lactic and its biodegradability. *Prog.in Polymer Science* 34, 99-124 (2009).
36. Duda, A., Penczek,S., Kowalski, A. & Libiszowski, J. Polymerization of ε-caprolactone and L-lactide initiated with stannous octoate and stannous butoxide – a comparison. *Macromolecule Symp.*153, 41-53 (2000).
37. Kowalski,A.,Duda, A. & Penczek, S. Kinetics and mechanism of cyclic esters polymerization initiated with tin (II) octoate, 1. Polymerization of ε-caprolactone. *Macromol. Rapid Commun.*19, 567-571 (1998).
38. Du, Y. J., Lemstra, P. J., Nijenhuis, A. J., van Aert, H. A. M. & Bastiaansen, C. ABA type copolymers of lactide with poly (ethylene glycol): Kinetic, mechanistic and model studies. *Macromolecules* 28, 2124-2132 (1995).
39. Schwach, G., Coudane, J., Engel, R. & Vert, M. J. More about the polymerization of lactides in the presence of stannous octoate. *Polym. Chem., Part A: Polym. Chem*. 35, 3431 (1997).
40. Kricheldorf,H. R. & Damrau, D. O. Polymerizations of L-lactide initiated with Zn (II) L-lactate and other resorbable Zn salts. *Makromol. Chem. Phys.*198,1753-1766 (1997).
41. Storey, R. F. & Taylor, A. E. Effect of stannous octoate on the composition, molecular weight, molecular weight distribution of ethylene glycol-initiated poly (ε-caprolactone). *J MacromolSci – Pure Appl. Chem.*A 35, 723-750 (1998).
42. Eguiburu, J. L., Fernandez-Berridi, M. J. & San Roman, J. Functionalization of poly(L-lactide) macromonomers by ring-opening polymerization of L-lactide initiated with hydroxyethyl methacrylate-aluminiumalkoxides. *Polymer* 36, 173-179 (1995).