RSC Advances




ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

# Nanolamellar triblock of poly D, L-lactide- δ-valerolactone- D, L-lactide with tuneable glass transition and crystallinity for drug delivery vesicle

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***Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX***

**DOI: 10.1039/b000000x**

Biodegradable triblock copolymer, poly D, L-lactide- δ-valerolactone- D, L-lactide, was synthesized by ring opening polymerization of δ-valerolactone and sequential addition of D, L-lactide monomer to the hydroxyl end functionalized poly δ-valerolactone macroinitiator and evaluated for its suitability as drug delivery vesicle.The effect of monomer ratio, catalyst and initiator concentration on the structure was investigated by using $^{1}$H NMR, $^{13}$C NMR, Fourier transform infrared spectroscopy and gel permeation chromatography techniques. $^{1}$H NMR confirmed the presence of D, L-lactide segment as terminal segment and δ-valerolactone as mid segment. $^{13}$C NMR was used to study the block sequencing and extent of transesterification. The crystallization of the triblock was retarded due to incorporation of D, L-lactide moiety at the chain end of poly δ-valerolactone segment as compared to the neat poly δ-valerolactone homopolymer. The glass transition temperatures of the two blocks shifted depending on the ratio of the two monomers. The triblock, having molecular weight lying between 5000 to 10000 Dalton, exhibited nanophase separated morphology having alternating stripes of amorphous and crystalline segments (3-6 nm) in transmission electron microscopy. The triblock, fabricated into microsphere having average diameter of 17.2 μm, was used for encapsulation of salicylic acid. The formation of pores on the surface of the microsphere facilitated the release of salicylic acid. The release profile displayed the characteristic of a potential carrier.

## Introduction

Increasing awareness to protect global health along with depleting fossil fuel reserve and non-biodegradability of commodity plastics foster the research for exploring biomaterials due to its wide availability and nontoxic residues. As a consequence, novel strategies to increase the use of biodegradable polymer in everyday life have attracted a great deal of attention to solve problem of time resistant polymeric waste. Aliphatic polyesters derived from lactones are well recognized as biodegradable polymers. Among them, polylactide is most widely studied biomaterial with huge demand in biomedicine industry[1], but certain limitations of polylactide[2] endeavor scientists to investigate other polyesters like poly ε-caprolactone, polyethylene glycol etc. Copolymerization with complementing monomers opens a lucrative scope for tailoring physical properties like strength and dimensional stability by adjusting the ratio of constituting block, adding new block. Structure-property relationship of several copolymers has been reported earlier from this laboratory[3,4]. Ring opening polymerization technique has been successfully employed for synthesizing copolymers of lactones like glycolide (GA), lactide (LA), β—butyrolactone, ε-caprolactone and 1,5-dioxepan-2-one[5-10]. The architecture of the copolymers was tailored to yield random, diblock, triblock, graft and star copolymer by controlling the sequence of addition, and varying the initiator catalyst system [11].

There are preliminary reports on homo polymerization of δ- valerolactone. Ring opening coordination insertion polymerization and living cationic polymerization have been used most efficiently for δ-valerolactone[12-14].The major hurdle is the cytotoxicity of

the catalyst residues limiting commercialization of such processes. Among the catalysts, tin octoate has been approved by American food and drug administration (FDA)[15], thus having preference over others. Research has also been accomplished in the field of copolymerization of δ-valerolactone with other lactone monomers and characterization of the polymers derived from the respective monomers[16,17]; however till date very few literature are available dealing with copolymer synthesis using δ-valerolactone and lactide[18], thus spurring our interest in this field. Lactide can be easily derived from corn starch and δ-valerolactone has been obtained as a byproduct during synthesis of adipic acid from tetrahydrofuran[19].The characteristics like glass transition, crystallinity, morphology of the homopolymers can be tailored by the copolymerization technique. The monomer ratio in the synthesized copolymer may efficiently control the degradation rate of the copolymer. The copolymer system can be successfully used as drug delivery system due to its biodegradable and biocompatible nature that has not been carried out before.

The state of the art application of biodegradable and biocompatible polymers is in the preparation of drug delivery vesicle, biomimetic implants and scaffold designing for tissue engineering. Another improvised system used for drug delivery is microsphere having the ability of encapsulating therapeutic agent. The copolymers from poly ε- caprolactone or poly ethylene glycol (PEG) in combination with glycolic acid and lactic acid appeared as a promising candidate for microsphere[20-25]. Several articles are reported on PEG system for micelle assisted drug delivery [26,27]. But crafting microspheres using triblock copolymer of δ- valerolactone and D, L- lactide has not established yet.

The present study basically consisted of two parts: in the first part, stepwise synthesis of new triblock copolymer, D, L-lactide- δ-valerolactone- D, L-lactide was executed. Although the copolymerization technique was well established in literature, it was manipulated in terms of catalyst, initiator, time and temperature. Since the triblock is new, the reactivity of the comonomers will be governed by these parameters. The triblock architecture of the copolymer is controlled by sequential addition of the monomers. The use of any organic solvent was excluded during the process of preparation, thus implementing more environment friendly methodology. The chemical composition was examined through $^{1}$H NMR, $^{13}$C NMR and Fourier transform infrared spectroscopy (FTIR) techniques. The crystallinity of the polymer was studied by wide angle X-ray diffraction (WAXD) in powder form. In addition, Gel permeation chromatography (GPC) was carried out for determining the molecular weights and their distribution. Thermal properties were evaluated using differential scanning calorimetry (DSC). The morphology of the block copolymer was thoroughly investigated using transmission electron microscopy (TEM). A detailed investigation of the properties is very essential to understand the performance of the resulting polymer. The paper highlights several factors which tailor molecular weight, crystallinity and thermal properties of the copolymer, that are not reported in the literature for such triblock polymer. The catalyst and initiator concentrations have been varied to study the effect of these on copolymerization reaction. Literature dealing with morphological study of biodegradable block copolymer is rather scanty[28, 29], which drives our interest to investigate the bulk morphology of the synthesized copolymer. The second part of the study dealt with successful preparation of microspheres from the copolymer, incorporation of salicylic acid in the microsphere and release study of salicylic acid from the microsphere in saline phosphate buffer (PBS) of pH 7.4. Field emission scanning electron microscopy (FESEM) was employed to establish the formation of the microspheres and UV-visible spectroscopy was used to carry out the release study.
Such comprehensive investigation involving various factors for this system has not been reported before, according to the authors' knowledge.

**Materials and methods**

D, L- lactide was used as received and stored and handled under nitrogen atmosphere in a glove box. δ-valerolactone and tin(II) 2-ethyl hexanoate were distilled under reduced pressure and stored under nitrogen environment. 1, 6-hexanediol was used as received and stored under vacuum. All the chemicals were purchased from Sigma – Aldrich, Germany. All other solvents were used as received without further purification.

$^1$H NMR spectra were recorded in Model AVANCE III 400 Ascend Bruker operating at 400 MHz and $^{13}$C NMR data were collected at 100 MHz and 400 MHz. The samples for NMR were prepared in $CDCl_3$ solution and chemical shifts were reported in δ (ppm) relative to the $^1$H signals from protic solvent (7.26 ppm for $CDCl_3$). The molecular weight distribution of the homopolymers and copolymers was measured by Agilent PLGPC 50 Integrated using PLgel 5µm Mixed- D column equipped with a refractive index detector using THF as solvent. The FTIR spectra were recorded on KBr pellets by using Perkin Elmer Spectrum 400 machine in a spectral range of 4000–530 $cm^{-1}$ with a total of 16 scans per sample. Wide angle X-ray diffraction analysis was carried out using Rigaku TT RAX 3XRD machine with $CuK_\alpha$ (0.154 nm) as radiation source at 50 KV. Differential scanning calorimetry was conducted in Perkin Elmer DSC8000 under nitrogen atmosphere. Samples, in hermetically sealed aluminium pans, were analyzed following the steps: the samples were equilibrated at 80 °C at 10 °C/min then cooled to -80 °C at 10 °C/ min followed by reheating to 80 °C at 2 °C/min and the glass transition temperature was reported in the second heating cycle. The morphological studies were executed using Tecnai G2 transmission electron microscopy at 120 KV in transmission mode. The samples were prepared by embedding into epoxy and then the region of interest was sectioned by diamond knife having 100 nm thickness. The sections were stained with $OsO_4$ stain for 4 hrs at 72 °C, followed by freshly prepared $RuO_4$ staining for 4 hrs.

**Synthesis of poly δ-valerolactone**

A typical procedure for synthesizing poly δ-valerolactone is reported here. δ-valerolactone (26.97 g, 0.2694 mol), and 1, 6-hexanediol (31.8 mg, 0.2694 mmol) were added in a 25 mL round bottom flask equipped with a Teflon – coated magnetic stirrer under nitrogen atmosphere. The sealed reaction vessel was then placed in an oil bath and heated up to 90 °C at a heating rate of 2 °C/min followed by addition of $Sn(Oct_2)$ (0.109 g, 0.2694 mmol). The reaction mixture was then heated to 120 °C for 48 hrs. After cooling, the solid reaction product was dissolved in dichloromethane and precipitated in excess methanol. The solvent was removed under reduced pressure at room temperature for 2 days. The sample was designated as D1. Time of reaction was varied from 12 hrs to 48 hrs. The Ratio of monomer (M) and initiator (I) concentration i.e. $[M]_0/[I]_0$ was varied from 333 to 2000, when the ratio of monomer (M) and catalyst ( cat) i.e. $[M]_0/[cat]_0$ ranged between 333 to 2000. The reaction parameters for synthesizing D0, D1, D2, D3, and D4 are summarized in Table 1. The product was characterized by FTIR, $^1$H NMR, $^{13}$C NMR and size extrusion chromatography (SEC). $^1$H NMR (400 MHz, $CDCl_3$, δ): 7.3, 4.1, 3.7, 2.4, 1.7.$^{13}$C NMR (400 MHz, $CDCl_3$, δ): 173.5, 171.6, 69.7, 68.1, 64.1, 33.9, 30.0, 28.2, 25.8, 22.5, 21.6, 19.3. Poly D, L-lactide homopolymer was also synthesized (see ESI† for details) and characterized by above techniques. $^1$H NMR (400 MHz, $CDCl_3$, δ): 7.3, 5.2, 3.8, 2.4, 1.6. $^{13}$C NMR (400 MHz, $CDCl_3$, δ): 169.6, 72.5, 69.4, 66.7, 20.5, 16.7, 15.8.

**Synthesis of D, L-lactide- δ-valerolactone- D, L-lactide triblock copolymer**

In the glove box, D1(3.16 g, 31.56 mmol) and D, L- lactide(3.17 g, 21.99 mmol) were added in a 25 mL round bottom flask equipped with a Teflon – coated magnetic stirrer under nitrogen atmosphere. The sealed reaction vessel was then placed in an oil bath and heated up to 90 °C followed by addition of $Sn(Oct_2)$ (0.01084 g, 0.0268 mmol). The reaction mixture was then heated to 140 °C for 8 hrs. The reaction product was then cooled to room temperature and dissolved in dichloromethane followed by precipitation in excess methanol. The recovered solid was dried under reduced pressure for 2 days. The sample was marked as DL15050. The resulting copolymer was thoroughly analyzed by FTIR, $^1$H NMR, $^{13}$C NMR and GPC characterization techniques. Several copolymers having variable feed composition were prepared using homopolymer as macroinitiator, synthesized at different $[M]_0/[I]_0$ and $[M]_0/[cat]_0$ ratios. The sample details are given in Table 1. $^1$H NMR (400 MHz, $CDCl_3$, δ): 7.3, 5.2, 4.1, 3.7, 2.3, 1.7, 1.6, 1.3. $^{13}$C NMR (400 MHz, $CDCl_3$, δ): 173.3, 169.6, 169.4, 169.1, 69.4, 69.2, 68.9, 68.3, 66.7, 65.0, 63.9, 33.7, 33.4, 33.1, 28.1, 27.9, 27.7, 21.4, 21.2, 20.5, 16.7, 16.6, 15.8.

**Table1** Sample details

| | Condition | Wt %ratio | Catalyst | Initiator | Remarks |
|---|---|---|---|---|---|
| D0 | Polymerization of δ- valerolactone at 120 °C for 48 hrs + 0.3 mol% catalyst, 0.3 mol% initiator | - | Tin octoate | 1,6-hexanediol | |
| D1 | Polymerization of δ- valerolactone at 120 °C for 48 hrs + 0.1 mol% catalyst,0.1 mol% initiator | - | Tin octoate | 1,6-hexanediol | |
| D2 | Polymerization of δ- valerolactone at 120 °C for 48 hrs + 0.05 mol% catalyst,0.05 mol% initiator | - | Tin octoate | 1,6-hexanediol | |
| D3 | Polymerization of δ- valerolactone at 120 °C for 48 hrs + 0.1 mol% initiator, 0.05 mol% catalyst | - | Tin octoate | 1,6-hexanediol | |
| D4 | Polymerization of δ- valerolactone at 120 °C for 12 hrs + 0.126 mol% initiator, 0.1mol% catalyst | - | Tin octoate | 1,6-hexanediol | |
| DL15050 | Polymerization of δ- valerolactone at 120 °C for 48 hrs + 0.1 mol% catalyst,0.1 mol% initiator, addition of D,L-lactide at 140 °C for 6 hrs+ 0.05 mol% cat | 50:50 | Tin octoate | 1,6-hexanediol | Variable composition taking D1 as macroinitiator |
| DL16634 | Polymerization of delta valerolactone at 120 °C for 48 hrs + 0.1 mol% catalyst,0.1 mol% initiator, addition of D,L-lactide at 140 °C for 6 hrs+ 0.05 mol% catalyst | 66 : 34 | Tin octoate | 1,6-hexanediol | |
| DL18020 | Polymerization of δ- valerolactone at 120 °C for 48 hrs + 0.1 mol% catalyst,0.1 mol% initiator, addition of D,L-lactide at 140 °C for 6 hrs+ 0.05 mol% catalyst | 80:20 | Tin octoate | 1,6-hexanediol | |
| DL25050 | Polymerization of δ- valerolactone at 120 °C for 48 hrs + 0.05 mol% catalyst, 0.05 mol%initiator, addition of D,L-lactide at 140 °C for 6 hrs+ 0.05 mol% catalyst | 50:50 | Tin octoate | 1,6-hexanediol | Variable composition taking D2 as macroinitiator |
| DL26634 | Polymerization of delta valerolactone at 120 °C for 48 hrs + 0.05 mol% catalyst,0.05 mol% initiator, addition of D,L-lactide at 140 °C for 6 hrs+ 0.05mol% catalyst | 66:34 | Tin octoate | 1,6-hexanediol | |
| DL28020 | Polymerization of delta valerolactone at 120 °C for 48 hrs + 0.05 mol% catalyst,0.05 mol% initiator, addition of D,L-lactide at 140 °C for 6 hrs+ 0.05 mol% catalyst | 80:20 | Tin octoate | 1,6-hexanediol | |
| D2L1 | Polymerization of δ- valerolactone at 120 °C for 48 hrs + 0.05 mol% catalyst,0.05 mol % initiator, addition of D,L-lactide at 140 °C for 6 hrs+ 0.02 mol% | 66 : 34 | Tin octoate | 1,6-hexanediol | |

| | | | | | |
|---|---|---|---|---|---|
| | catalyst | | | | |
| D2L2 | Polymerization of δ- valerolactone at 120 °C for 48 hrs + 0.05 mol% catalyst, 0.05 mol% initiator, addition of D,L-lactide at 140 °C for 6 hrs+ 0.05 mol% catalyst | 66 : 34 | Tin octoate | 1,6-hexanediol | |
| D2L3 | Polymerization of δ- valerolactone at 120 °C for 48 hrs + 0.05 mol% catalyst, 0.05 mol% initiator, addition of D,L-lactide at 140 °C for 6 hrs+ 0.126 mol% catalyst | 66 : 34 | Tin octoate | 1,6-hexanediol | |
| DL4060 | Polymerization of δ- valerolactone at 120 °C for 48 hrs + 0.3 mol% catalyst, 0.3 mol%initiator, addition of D,L-lactide at 140 °C for 6 hrs+ 0.126 mol% catalyst | 40:60 | Tin octoate | 1,6-hexanediol | Variable composition taking D0 as macroinitiator |
| DL6040 | Polymerization of δ- valerolactone at 120 °C for 48 hrs + 0.3 mol% catalyst, 0.3 mol% initiator addition of D,L-lactide at 140 °C for 6 hrs+ 0.126 mol% catalyst | 60:40 | Tin octoate | 1,6-hexanediol | |
| DL7030 | Polymerization of δ- valerolactone at 120 °C for 48 hrs + 0.3 mol% catalyst, 0.3 mol% initiator addition of D,L-lactide at 140 °C for 6 hrs+ 0.126 mol% catalyst | 70:30 | Tin octoate | 1,6-hexanediol | |

**Preparation of microspheres from D, L-lactide- δ-valerolactone- D, L-lactide triblock copolymer containing salicylic acid**

Salicylic acid loaded microspheres were prepared by solvent evaporation technique in oil-in-water emulsion. First both salicylic acid (200 mg) and D, L-lactide- δ-valerolactone- D, L-lactide triblock copolymer (400 mg) were dissolved in 10 mL of dichloromethane and sonicated for 15 minutes. Then the solution was added drop wise to an aqueous medium containing 0.5 wt% twin 20 (polyethylene glycol sorbitan monolaurate) while mixing vigorously at 1000 rpm using a mechanical stirrer. The stirring was continued for 1 hr in order to evaporate dichloromethane and the microspheres were collected by centrifugation at 12000 rpm. The salicylic acid loaded microspheres were thoroughly washed with water and dried in vacuum oven for 2 days.

**In vitro release study of salicylic acid from loaded triblock copolymeric microsphere**

The in vitro release study was performed in saline phosphate buffer (PBS) of pH 7.4. 0.65 mg of salicylic loaded microspheres was dispersed in 100 mL PBS buffer. The release medium was placed in an orbital shaker at 160±10 rpm and an aliquot of 0.5 mL, taken out from the medium at set time intervals for analysis, was replaced by equal volume of fresh buffer solution. The concentration of salicylic acid was measured by using UV-vis spectrophotometer (Model: UV-2550, Shimadzu). Salicylic acid showed a strong absorption band at 294 nm associated with a weak absorption at 229 nm. The absorbance of PBS buffer was negligible in this region. The concentration of the salicylic acid in the release medium was relatively dilute, and hence, the solution was assayed spectrophotometrically at 294 nm, the stronger absorption band, at predetermined time intervals.

The microspheres were examined under a FESEM (Hitachi, S-4800 FESEM) at an accelerating voltage of 10 KV. Samples of microsphere before and after release were prepared by dropping a microparticle suspension on double sided carbon adhesive tape adhered on the stub and coated with platinum using Hitachi E-1010 Ion Sputter system. Fourier transform infrared spectroscopy (FTIR) in KBr mode was also employed to confirm the incorporation of salicylic acid in microsphere. Thermogravimetric analysis was carried out with TA instruments SDT Q600 system at a ramp rate of 10 °C/min under nitrogen atmosphere from room temperature to 500 °C.

## Results and Discussion

### Synthesis and characterization of poly δ-valerolactone

The bulk ring opening polymerization technique was adopted for the synthesis of poly δ-valerolactone homopolymer using tin 2-ethyl hexanoate as catalyst and 1, 6-hexanediol as initiator at 120 °C for 48 hrs. A series of reactions were investigated by varying the monomer to initiator ratio from 333 to 2000, where the catalyst to monomer ratio was also varied in a similar manner (Table 1). Typical yield was between 68 to 88% depending on the composition of the mixture (Table 2). An aliquot of the cooled reaction mixture was thoroughly analyzed by $^{1}$H NMR, $^{13}$C NMR, and FTIR spectroscopic techniques.

**Table 2** % conversion, $M_n$ and PDI determination for homo poly δ –valerolactone

| | CONDITION | $[M]_0/[I]_0$ | $[M]_0/[cat]_0$ | % conversion | $M_n$(SEC) Dalton | $M_n$(NMR) g/mol | PDI |
|---|---|---|---|---|---|---|---|
| D0 | 120 °C, 48 hrs | 333 | 333 | 68.1 | 5100 | 4550 | 1.39 |
| D1 | 120 °C, 48 hrs | 1000 | 1000 | 70.5 | 7240 | 7400 | 1.37 |
| D2 | 120 °C, 48 hrs | 2000 | 2000 | 69.5 | 8200 | 7150 | 1.41 |
| D3 | 120 °C, 48 hrs | 1000 | 2000 | 68.9 | 8730 | 6700 | 1.45 |
| D4 | 120 °C, 12 hrs | 794 | 1000 | 88.0 | 11700 | 8500 | 1.49 |

Fig. 1a shows typical $^{1}$H NMR spectra of the poly δ-valerolactone homopolymers. The signals obtained for representative homopolymer D1, are: $^{1}$H NMR (400MHz, $CDCl_3$, δ): 7.3 (s, 4H), 4.1 (m, 147H), 3.7 (t, 4H), 2.4 (m, 159H) and 1.7 (m, 330H). In $^{1}$H NMR (Fig. 1a), protons (e) adjacent to the acyl oxygen appearing at δ- 4.08-4.15 ppm, protons (b) next to the carbonyl carbon at δ-2.3-2.4 ppm and methylene protons (c, d) at δ- 1.6- 1.7 ppm give evidence for formation of poly δ-valerolactone. Only a small low intensity peak is noticed at δ- 3.9 ppm indicating presence of terminal methylene (e) protons of δ-valerolactone unit, attached to the hydroxyl chain end. Participation of 1,6-hexanediol as initiator is also apparent from the spectrum showing two terminal methylene resonances at δ- 3.6 ppm (1), but the other representative peaks (2, 3) merge with the peaks for protons (b, c, d) of poly δ-valerolactone. The $^{1}$H NMR spectra obtained for D0, D2, D3, D4 are similar to that for D1.

The $^{13}$C NMR spectra of the corresponding homopolymers are collated in Fig. 1b. The signals for representative poly δ –valerolactone homopolymer D1, are as follows: $^{13}$C NMR (400 MHz, $CDCl_3$, δ): 173.5, 171.6, 69.7, 68.1, 64.1, 33.9, 30.0, 28.2, 25.8, 22.5, 21.6, and 19.3. The signals assigned are - carbonyl carbon (a) appearing at 173.0 ppm, methylene carbon (e)adjacent

to the acyl oxygen at 69.0 ppm, methylene carbon (b) attached to carbonyl group at 30.0 ppm, other two methylene carbons c, d appearing at 22.0 ppm and 19.0 ppm respectively. Thus, the results of $^{13}C$ NMR are consistent with that of $^{1}H$ NMR, clearly indicating success of the reaction. Incorporation of 1, 6-hexanediol is also evident from the signals at 64.0 ppm showing the presence of terminal methylene carbon (1) adjacent to oxygen, 33.9 ppm and 25.8 ppm attributed to the internal methylene carbons 2, 3 respectively of the 1, 6-hexanediol unit. A quantitative upfield shift (e.g. from δ-173.5 ppm (a) to δ-171.69 ppm (a') in C=O region) has been observed for the segment of poly δ-valerolactone, attached to the 1, 6-hexanediol from the repeating segment. The $^{13}C$ NMR spectra of D0 (Fig. S1 ESI†), D2, D3 (Fig. S1 ESI†) and D4 also show all the representative peaks as observed for D1.

The characteristic frequencies observed for δ–valerolactone monomer and a series of homopolymers, in FTIR spectroscopy are shown in Fig. S2. The broad region at 3530 $cm^{-1}$ for OH stretching [30] in the monomer increases in the spectra of homopolymers supporting the ring opening of δ–valerolactone. The other characteristic vibrational frequencies like 1730 $cm^{-1}$ for C=O stretching, 2900 $cm^{-1}$ for $CH_2$ stretching, , 1154-1172 $cm^{-1}$ for C-O-C bond and 1041 $cm^{-1}$ for O-$CH_2$ stretching validate the formation of poly δ–valerolactone. These are in line with literature[31]. The peak at 1185 $cm^{-1}$ corresponding to C-O-C bond stretching in the monomer, broadens upon polymerization along with a small shift to 1180 $cm^{-1}$, as clearly shown in Fig. S2 (ESI†). The band at 1106 $cm^{-1}$, assigned for C-O-Sn bond formation[32], is present in all the δ–valerolactone homopolymers, which is totally absent in the monomer. All these justify the success of ring opening polymerization.

After precipitation of the polymer, the molar mass characteristics were measured by SEC (Fig. S3 ESI†) using polystyrene standards (Table 2). The δ-valerolactone with variable block length was synthesized by altering the ratio of $[M]_0/[I]_0$ and $[M]_0/[cat]_0$ at reaction temperature of 120 °C for 48 hrs. A monomodal mass distribution with PDI ranging from 1.37-1.49 was observed for all the homopolymers. From $^{1}H$ NMR spectra, the molecular weight of the homopolymer was calculated from integral ratio of methylene protons at δ-4.1 ppm (e) of δ-valerolactone and methylene protons of 1,6-hexane diol at δ-3.6 ppm (1) (Fig. 1a). The value of $M_n$ from $^{1}H$ NMR was in close proximity with that obtained from GPC (Table 2).

The effect of catalyst concentration on the polymerization of δ-valerolactone was studied keeping the $[M]_0/[I]_0$ ratio constant (1000). The catalyst concentration $[M]_0/[cat]_0$ was varied from 1000 (for D1) to 2000 (for D3), when it showed an increase in molecular weight and PDI as determined from SEC. The role of initiator was evaluated when the catalyst concentration $[M]_0/[cat]_0$ was kept constant (1000). If the $[M]_0/[I]_0$ ratio decreased from 1000 (for D1) to 794 (for D4), higher conversion and molecular weight were achieved in lesser time (12 hrs).

Actually, optimization of catalyst and initiator concentration is very crucial for the polymerization. Here 1, 6-hexane diol reacts with tin 2- ethyl hexanoate $Sn(Oct)_2$ to generate an alkoxide initiator $Sn(OR)_2$. It can also act as a chain transfer agent, and thereby can effectively control the molecular weight [33]. If the concentration of tin 2- ethyl hexanoate $Sn(Oct)_2$ increases, it leads to randomization in copolymer sequencing. Here several polymerizations were carried out with varying both $[M]_0/[I]_0$ and $[M]_0/[cat]_0$. All the parameters are tabulated in Table 2. The system having $[M]_0/[I]_0 = 333$ and $[M]_0/[cat]_0 = 333$ was found to be least effective among all the systems in terms of conversion and molecular weight, whereas highest conversion has been achieved with $[M]_0/[I]_0 = 794$ and $[M]_0/[cat]_0 = 1000$ system in shorter time.

A series of poly D, L-lactide homopolymers (L1, L2, L3 and L4) were also synthesized and characterized (see ESI† Fig. S4 –S5). $^{1}H$ NMR spectra of all the homopolymers show the representative peaks confirming the ring opening polymerization of poly D, L-lactide. Fig. S4 shows typical $^{1}H$ NMR spectra of the poly D, L-lactide homopolymers. The signals obtained for representative homopolymer L1, are as follows: $^{1}H$ NMR (400 MHz, $CDCl_3$, δ): 7.3 (s, 4H), 5.2 (m, 141H), 3.8 (t, 4H), 1.6 (m, 434H). In $^{1}H$ NMR (Fig. S4), the methine protons (A) at δ = 5.2 ppm and methyl protons (B) appearing at δ = 1.6 ppm give evidence for

formation of poly D, L-lactide. Only a small low intensity peak is noticed at δ- 4.3 ppm indicating presence of terminal methine (A) protons of D, L-lactide unit, attached to the hydroxyl chain end[6]. Participation of 1, 6-hexanediol as initiator is also apparent from the spectrum showing two terminal methylene resonances at δ- 3.7 ppm (1), but the other representative peaks (2,3) merge with the peaks for protons (B) of poly D, L-lactide.

The $^{13}C$ NMR spectra of the corresponding homopolymers are collated together in Fig. S5. The signals for representative poly D, L-lactide homopolymer L1, are as follows: $^{13}C$ NMR (400 MHz,$CDCl_3$, δ) : 169.6, 72.5, 69.4, 66.7, 20.5, 16.7, 15.8.The signals assigned are - carbonyl carbon (C) appearing at 169.0 ppm, methine carbon (A) at 69.0 ppm and methyl carbon (B) at 16.0 ppm. Thus, the results of $^{13}C$ NMR are consistent with that of $^{1}H$ NMR, clearly indicating success of the reaction. Incorporation of 1, 6-hexanediol is also evident from the signals at 66.0 ppm showing the presence of terminal methylene carbon (1) adjacent to oxygen and 20.5 ppm attributed to the internal methylene carbons (3) of the 1, 6-hexanediol unit. As shown in Table S1 (ESI†), the GPC molecular weight of the various polymers lies in the range of 11000-17000 Dalton. The NMR results corroborate with the observations for GPC. The above results are necessary for understanding the triblock copolymer made from D, L-lactide.

**Synthesis and characterization of D, L-lactide- δ-valerolactone- D, L-lactide triblock copolymer**

D,L-lactide- δ –valerolactone - D, L-lactide copolymers were prepared by ring opening bulk polymerization technique using poly δ-valerolactone as macroinitiator and tin 2-ethyl hexanoate as catalyst as shown in Scheme 1.

The precipitated copolymers were analyzed by $^{1}H$ NMR, $^{13}C$ NMR, FTIR and SEC. The $^{1}H$ NMR spectrum of a DL15050 copolymer is shown in Fig. 2a. The spectrum contains the signals of D,L-lactide as well as δ –valerolactone, given as follows: $^{1}H$ NMR (400 MHz,$CDCl_3$, δ): 7.3 (s, 4H), 5.2 (m, 240H), 4.1(m, 535H), 2.3 (m, 588H), 1.7 (m, 1169H), 1.6 (m, 786H), 1.3 (s, 4H). The proton signals at 4.1 ppm, 2.3 ppm and 1.6-1.7 ppm confirm the presence of δ –valerolactone unit as discussed before. The other two resonances at δ-5.2 ppm and 1.3 ppm account for methine proton (A) and methyl protons (B) respectively.

The terminal methylene protons (δ-3.9 ppm) attached to end hydroxyl group in poly δ-valerolactone is replaced by the hydroxyl terminus methine proton of PLA (δ-4.3 ppm) upon chain extension[32], indicating quantitative chain initiation efficiency (Fig. 2a). In course of polymerization process, chain transfer can occur simultaneously[34] where the active chain end of polylactide (PLA) segment can undergo transesterification reaction with poly δ-valerolactone unit generating δ- valerolactone chain end. This phenomenon will lead to randomization of chain segments facilitating formation of random copolymer or multiblock copolymer instead of desired triblock. The absence of δ- valerolactone chain end (δ-3.9 ppm) (Fig. 2b) supported the fact that very limited transesterification has taken place.

Fig. 2c represents the $^{13}C$ NMR spectrum of a typical block D, L-lactide- δ –valerolactone - D, L-lactide copolymer DL15050. The signals obtained for the corresponding copolymer are as follows: $^{13}C$NMR (400MHz,$CDCl_3$, δ): 173.3, 169.6, 169.4, 169.1, 69.4, 69.2, 68.9, 68.3, 66.7, 65.0, 63.9, 33.7, 33.4, 33.1, 28.1, 27.9, 27.7, 21.4, 21.2, 20.5, 16.7, 16.6, 15.8 ppm. In $^{13}C$ NMR, the signals indicating the presence of δ–valerolactone segment are as follows: at 173.3 ppm for carbonyl carbon (a), at 68.0 ppm for carbon (e) adjacent to the acyl oxygen, at 28.1 ppm for methylene carbon (b) attached to carbonyl group and other two internal methylene carbons (c, d) appearing at 21.4, 20.5 ppm. The additional peaks for LA repeating unit appeared at 169.5 ppm for C=O (C), 69.0 ppm for methine carbon (A) and 15.8 ppm for $–CH_3$ (B), whereas the signals at 64.0 ppm and 34.0 ppm establishing the incorporation of 1,6 -hexanediol in the main chain. This support the formation of the copolymer. Multiple signals in the C=O region (δ-173.3, 169.6, 169.4, 169.1ppm) confirm the block formation. 168-173 ppm represents the carbonyl signals for different monomer sequences [35]. A sharp peak at 173.3 ppm and several low intensity signals in the region of 169.0 ppm were observed for all the copolymers shown in Fig. 2d.

For homopolymers poly δ-valerolactone and poly D, L- lactide, the C=O resonances were observed at 173.7 ppm and 169.1 ppm respectively. But in the copolymer, plural peaks were observed instead of single peaks. A downfield shift of additional carbonyl

signals was observed for lactyl unit due to presence of δ-oxyvalery unit appearing as triads LLV, VLL, VLV (Fig. 2d) whereas, an additional upfield signal has been noticed for carbonyl group of δ- valerolactone unit corresponding to the triads LLV and LVL[36]. In order to establish the formation of triblock, we have synthesized a copolymer of δ –valerolactone and D, L-lactide by simultaneous addition (DVL-S-DLLA). A comparison of $^{13}C$ NMR spectra in the carbonyl region between DVL-S-DLLA and all the copolymers synthesized by step addition showed (Fig. 2d) that there were additional peaks in the case of DVL-S-DLLA. These additional peaks, generated due to random cross propagation reactions between D,L-lactide and δ-valerolactone active chain ends, were completely absent in the synthesized block copolymers. Thus, analysis of C=O signals of the copolymer verifies the triblock sequence of δ–oxyvalery and lactyl unit. As in the second step of polymerization δ-valerolactone monomer is absent, transesterification is the only route that can lead to randomization of the chain sequence. The existence C=O signal at 170 ppm for VLV triad gives evidence for transesterification[37]and the extent of transesterification is represented quantitatively by the relative intensity of VLV triad. No transesterification occurs in the case of DL15050, DL16634 and DL18020. For other triblock copolymers, the extent of transesterification calculated is as follows: for DL25050 7.2 %, for DL26634 13.3%, for DL28020 14.6%, for D2L1 9.4%, for D2L3 10.1%. So, limited transesterification was observed for all the synthesized block copolymers, as confirmed by the $^{13}C$ NMR spectra.

**Fourier transform infrared spectroscopy (FTIR) analysis of copolymer**

The FTIR spectra of a series of triblock copolymers (DL15050, DL16634 and DL18020) were compared with the corresponding homopolymer (D1) and monomer, shown in Fig. S6 (ESI†). The synthesized copolymer contained all the representative peaks for δ-valerolactone and D, L-lactide. The broad region at 3560 $cm^{-1}$ for OH stretching increased on copolymerization, implying the success of the reaction. $\nu_{CH3}$ (2965 $cm^{-1}$), representative frequency for D, L-lactide, overlapped with $\nu_{CH2}$ of δ-valerolactone. The peak areas corresponding to the signals at 1326 $cm^{-1}$ for C-H bending and at 1730 $cm^{-1}$ for C=O stretching, showed an increase on polymerization. The peak at 1106 $cm^{-1}$, attributed for C-O-Sn bond formation, was absent in the copolymers DL15050, DL16634 and DL18020 indicating replacement of Sn. The band at 1176 $cm^{-1}$, for C-O-C stretching in D1, shifted to 1187 $cm^{-1}$ in the case of DL15050, but for others it remained same. The other relevant vibrational frequencies like $\nu_{C=O}$, $\nu_{COO}$ were similar to those for δ- valerolactone.

**GPC analysis**

Comparison between SEC chromatograms of poly δ –valerolactone prepolymer and D,L-lactide- δ –valerolactone - D, L-lactide triblock copolymers is shown in Fig. S7 (ESI†). The shift of the chromatograms of the copolymers towards the shorter retention time confirmed the chain extension reaction in presence of D, L- lactide monomer. In this work, poly δ-valerolactone was synthesized first, then it acted as a bifunctional hydroxyl capped macroinitiator for ring opening polymerization of D, L –lactide, leading to formation of triblock D,L-lactide- δ-valerolactone- D,L-lactide. Table 3 showed the feed composition, copolymer composition, $M_n$ and PDI for a series of the copolymers. The poly δ-valerolactone and D, L-lactide feed ratio was varied to alter the block length of D, L- lactide. DL15050, DL16634, DL18020 were synthesized using D1 as macroinitiator. The $M_n$ for these copolymers ranged between 10433 to 11056 Dalton. For other series DL25050, DL26634, DL28020 using D2 as macroinitiator, there was a sharp rise in the $M_n$, as the wt% of D, L-lactide was increased in the copolymer composition. For D2L1, D2L2, D2L3, the macroinitiator was D2, but the $[M]_0/[cat]_0$ ratio was varied from 5000 to 794 in the second step of polymerization i.e. addition of D,L-lactide keeping the monomer ratio 66:34. As the $[M]_0/[cat]_0$ ratio decreased, $M_n$ increased. Among the homopolymers, D1 and D2 were used as macroinitiator for further reaction with D, L-lactide with a feed ratio of 50:50. The molecular weight (from SEC) of DL15050 was little higher than that of DL25050. DL15050 contains more δ-valerolactone segment (61%) than DL25050 (59%).

**Table 3** Copolymer compositions, $M_n$ and PDI determination for D, L-lactide- δ –valerolactone - D, L-lactide

| | Wt% of lactide in monomer (theoretical) | Wt% of lactide in polymer (experimental) | Wt% of δ-valerolactone in monomer (theoretical) | Wt% of δ-valerolactone in polymer (experimental) | Molecular weight(g/mol) determined from SEC | PDI |
|---|---|---|---|---|---|---|
| D0 | - | - | - | - | 5100 | 1.39 |
| D1 | - | - | - | - | 7240 | 1.23 |
| DL15050 | 50 | 39 | 50 | 61 | 10400 | 1.32 |
| DL16634 | 34 | 22 | 66 | 78 | 11000 | 1.49 |
| DL18020 | 20 | 10 | 80 | 90 | 10600 | 1.45 |
| D2 | | | | | 8200 | 1.85 |
| DL25050 | 50 | 41 | 50 | 59 | 9400 | 1.23 |
| DL26634 | 34 | 32 | 66 | 68 | 8300 | 1.40 |
| DL28020 | 20 | 12 | 80 | 88 | 5500 | 1.37 |
| D2L1 | 34 | 20 | 66 | 80 | 7680 | 1.39 |
| D2L2 | 34 | 32 | 66 | 68 | 9400 | 1.23 |
| D2L3 | 34 | 23 | 66 | 77 | 10100 | 1.33 |

**Wide angle X-ray diffraction (WAXD)**

Fig. 3a-3b represent the X-ray diffractograms of the homopolymers and the copolymers with variable composition of δ-valerolactone and D, L- lactide. All the WAXD profiles exhibited well resolved diffraction peaks in the 2θ range of 0-40°. The X-ray diffractogram for poly D, L- lactide shows a broad hump indicating amorphous nature of the polymer, whereas one intense major peak at 21.7° and a smaller peak at 24.4° are observed for poly δ-valerolactone. The crystallographic analysis clarified that poly δ-valerolactone acquired orthorhombic unit cell structure[38]. The homopolymers, D0, D1, D2 have a crystallinity of 33.3%, 28.5% and 29.8% respectively. In copolymers, similar diffraction pattern, indicating contribution of crystalline poly δ-valerolactone is observed. But the presence of D, L- lactide was reflected in reducing the cyrstallinity on increasing the D, L-lactide concentration in the copolymer. Incorporation of D, L-lactide reduced the crystallization ability of poly δ-valerolactone[39] (Fig. 3c). There was a sharp rise in the $M_n$, as the D, L-lactide composition was increased in the copolymer composition (Table 3), but crystallinity showed a reverse trend. The fall in crystallinity with increasing the D, L-lactide block length was due to the amorphous nature of D, L-lactide (Fig. 3c).

The crystallite size was calculated using Scherrer method and the lattice strain was determined using Williamson- Hall isotropic strain model( W-H- ISM)[40].

Scherrer equation gives the mean crystallite size as follows:

$L_c = k \lambda / \beta \cos \theta$ (1)

where, $\lambda$ = the wavelength of $CuK_\alpha$ = 0.154nm, $\beta$ = Full width at half maximum (FWHM) for the reflection at 21.7°.

The W-H- ISM is framed considering two factors: crystallite size and lattice strain assuming that the strain in the crystal lattice is uniform. This equation is shown as follows:

$\beta \text{ Cos } \theta = k\lambda / L_c + 4 \varepsilon \text{ Sin } \theta$ (2)

where, k is the shape factor with a magnitude of 0.9, $\varepsilon$ is the lattice strain. A plot of $\beta\text{Cos}\theta$ in the y-axis vs. $4\text{Sin}\theta$ in the x-axis gives the magnitude of lattice strain ($\varepsilon$) as slope and the crystallite size $L_c$ is evaluated from the intercept. All the values of Lattice strain and crystallite size, % crystallinity for the polymers are compiled in Table 4.

The crystallite size increases in general as the block length of D, L-lactide segment increases and lattice strain also follows the same trend.

**Table 4** Crystallite size, lattice strain and %crystallinity

| Sample | Crystallite Size | | Lattice Strain | % crystallinity |
|---|---|---|---|---|
| | Scherrer Method | | (W-H Method) ($x10^{-3}$) | |
| | 2θ(°) | Lc (nm) | | |
| D1 | 21.8 | 18.64 | 3.41 | 28.5 |
| DL18020 | 21.7 | 16.41 | 4.69 | 24.0 |
| DL16634 | 21.8 | 16.50 | 9.89 | 19.5 |
| DL15050 | 21.8 | 16.78 | 13.22 | 13.7 |
| D2 | 21.8 | 17.66 | 3.82 | 29.8 |
| DL28020 | 21.7 | 16.44 | 6.17 | 24.0 |
| DL26634 | 21.8 | 16.47 | 6.36 | 17.0 |
| DL25050 | 21.7 | 18.09 | 6.54 | 15.0 |
| D0 | 21.8 | 25.93 | 12.97 | 33.3 |
| DL7030 | 21.8 | 16.89 | 12.37 | 19.4 |
| DL6040 | 21.7 | 19.68 | 19.68 | 21.3 |
| DL4060 | 21.8 | 34.14 | 13.04 | 12.6 |

**Thermal analysis**

The DSC thermograms of some representative samples of D, L-lactide- δ-valerolactone- D, L-lactide triblock copolymer are shown in Fig. 4 and the values of glass transition temperature of the copolymers are given in Table 5. The data revealed two glass transition temperatures indicating presence of two blocks. The glass transition temperature of poly δ-valerolactone appeared around -62.0 °C and for poly D, L- lactide, the $T_g$ was around 40.5 °C. All the copolymers show two glass transition temperatures

which shift depending on the block length of δ-valerolactone and D, L-lactide segment. The $T_g$ of δ-valerolactone segment shifts towards higher value (in the range of -47.0 °C to -33.0 °C), whereas, the $T_g$ of D,L-lactide segment shifts towards lower value (in the range of -33.0 °C to 4.19 °C). Higher block length of poly D, L-lactide shifts the $T_g$ of δ-valerolactone towards higher value, clearly indicating the $T_g$ of the block copolymer depends on the segmental length of poly D, L-lactide. All the copolymers melt in the range 51 °C to 66 °C.

The multimodal melting endotherms were observed for the copolymers envisioning broad distribution of the crystallite size. This occurs due to microphase separation in the melt state because of chemical incompatibility between the blocks followed by crystallization. When the microstructure of the copolymer is solely crafted by crystallization of one block, the crystallizable component can be subdivided forming the microdomains which appear to be higher than the number of active heterogeneities present. The multimodal melting endotherm is mainly evident for low molecular weight copolymer [41].

**Table 5** Thermal properties of the copolymer

| sample | $T_g$(δ-valerolactone) ° C | $T_g$ ( D, L-lactide) ° C |
|---|---|---|
| D1 | -62.0 | - |
| L1 | - | 40.5 |
| DL15050 | -32.8 | -12.4 |
| DL16634 | -41.2 | -32.7 |
| DL18020 | -46.8 | -32.4 |
| DL25050 | -37.4 | -22.2 |
| DL26634 | -36.3 | -3.1 |
| DL28020 | -52.7 | -29.3 |
| DL4060 | -35.6 | 20.8 |
| DL6040 | -66.9 | 4.2 |

**Morphological analysis**

The TEM micrographs of DL15050, DL16634 and DL18020 in toluene and DL15050 in chloroform are shown in Fig. 5. All the samples show uniform lamellar morphology having stripes of alternating contrast. From WAXD study, it is evident that the block copolymer contains amorphous poly D, L-lactide domains and crystalline poly δ-valerolactone domains. During staining, the amorphous regions of poly D, L-lactide were stained preferentially which appeared dark and the poly δ-valerolactone segment appeared bright under TEM. The domain size ranges between 3-6 nm. The TEM images obtained are similar to those observed for poly L-lactide – polymenthide - poly L-lactide triblock copolymer [41]. But the domain size is much lower for poly D, L-lactide-poly δ-valerolactone- poly D, L-lactide copolymer compared to poly L-lactide- polymenthide - poly L-lactide triblock copolymer.

**Characterization of salicylic acid loaded microspheres**

The FESEM micrographs of salicylic acid loaded microspheres, taken before and after release are shown in Fig. 6. The microspheres adopted a regular spherical morphology having an average diameter of 17.2 μm. Before release, surface of the

microspheres shows a smooth morphological pattern as shown in Fig. 6b. In buffer medium (PBS pH 7.4), salicylic acid releases, generating porous nature on the surface of the microsphere. The small pores as evident from Fig. 6d have dimension in the range of 1-4 μm supporting that the release of salicylic acid is favored by the degradation of copolymer on microsphere surface.

FTIR spectra (Fig. 7) gives evidence for encapsulation of salicylic acid exhibiting a peak at 1617cm$^{-1}$ for aromatic C=C stretching without distinct shift which indicates no chemical interaction has taken place between the copolymer and salicylic acid. Pristine salicylic acid showed maximum degradation temperature around 198 °C (shown in Fig. S8 inset ESI†) and the heat flow curve, as well as the derivative thermogram of salicylic acid loaded microsphere exhibited a hump around 202 °C indicating degradation of salicylic acid. Thermogravimetric analysis of the degradation curve confirmed 20% loading of salicylic acid within the microsphere at 202 °C (Fig. S8 ESI†). The release profile for salicylic acid loaded microspheres in phosphate buffer medium was studied for two samples DL16634 and DL18020 and the results are summarized in Fig. 8. For both the samples, initially a burst release was observed which increased with time and became steady after 24 hrs. For DL16634, 10.3% was released after 2 hrs which gave 12.2% after 24 hrs. The release rate of drug from salicylic acid loaded DL28020 was slower than that of DL16634 i.e. 8.8% after 2 hrs and only 10.1% after 24 hrs. An initial burst release occurred probably due to drug attached to microsphere surface and later the release is governed by diffusion [42] which is suppressed by the hydrophobic nature of the copolymer inhibiting the diffusion of water in the core and diffusion of salicylic acid into medium.

**Conclusions**

Novel D, L-lactide- δ- valerolactone- D, L-lactide copolymer was successfully synthesized and characterized exhaustively by various techniques. The sequential synthesis procedure adopted for D, L-lactide- δ- valerolactone- D, L-lactide showed the formation of hydroxyl end functionalized poly δ- valerolactone by the presence of small peak at 3.9 ppm, detected by $^{1}$H NMR, which disappeared upon addition of D, L-lactide moiety in the second step of polymerization. A peak at 4.3 ppm corresponding to D, L-lactide chain end appeared in the $^{1}$H NMR spectra. The success of the reaction was also ascertained by the broadening of peaks in the OH-stertching region at 3560 cm$^{-1}$ and carbonyl region at 1730 cm$^{-1}$. The reaction conditions for synthesis of poly δ-valerolactone were optimized in terms of initiator and catalyst concentrations and ring opening polymerization of δ-valerolactone at 120 °C for 12 hrs having $[M]_0/[I]_0 = 794$ and $[M]_0/[cat]_0 = 1000$ was found most effective. The block sequencing determined from carbonyl region of $^{13}$C NMR revealed that no transesterification was observed for DL15050, DL16634 and DL8020.Thorough analysis of $^{13}$C NMR and GPC results showed that the molecular weight varied as a function of block length, initiator/ catalyst ratio and extent of transesterification. The molecular weight increased as the ratio of D, L-lactide segment increased, but due to its amorphous nature it reduced the crystallinity as evident from WAXD analysis. Differential scanning calorimetry showed two glass transition temperatures, characteristic feature of a block copolymer. But the glass transition temperatures shifted towards lower or higher value on variation in the block length of the copolymers. The copolymer adopted lamellar morphology with alternating stripes showing the microphase separation, where the more crystalline poly δ- valerolactone moiety appeared as bright region and the comparatively darker domains assigned to amorphous poly D, L-lactide segment. It is imperative from the thermogravimetric analysis and FTIR spectra that the triblock microsphere could successfully encapsulate salicylic acid. In presence of buffer medium PBS pH 7.4, the salicylic acid is released from microsphere forming small holes on the surface of the microsphere and the release profile clearly exhibited its success as potential drug delivery system.

## Notes and references

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†Electronic Supplementary Information (ESI) available: [Synthesis of PolyD,L-lactide, FTIR spectra, GPC chromatograms, NMR spectra, TGA thermogram, Table]. See DOI: 10.1039/b000000x/

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**Figure captions:**

**Fig. 1a** $^{1}$H NMR Spectra of δ-valerolactone homopolymers D0, D1, D2, D3 and D4 and inset showing a small peak at 3.9ppm for D1.

**Fig. 1b** $^{13}$C NMR Spectra of poly δ-valerolactone homopolymers D1, D2 and D4 and inset showing expanded carbonyl region for D1.

**Fig. 2a** $^{1}$H NMR Spectra of a representative copolymer, DL15050.

**Fig. 2b** $^{1}$H NMR spectrum of D1 showing signal around 3.9ppm and $^{1}$H NMR spectra for DL15050, DL16634, DL18020 showing signal around 4.3ppm in the expanded region.

**Fig. 2c** $^{13}$C NMR Spectra of representative copolymer DL15050.

**Fig. 2d** $^{13}$C NMR spectra for copolymers showing the expanded C=O region (169-173 ppm).

**Fig. 3** (a)WAXD patterns for homopolymers D1, D2 and D3, (b) A comparison of WAXD patterns between homopolymer poly δ –valerolactone( PVL) and poly D, L- lactide ( PLA) and copolymers DL15050, DL16634, DL18020,(c) %crystallinity variation with increasing concentration of δ –valerolactone showing for D0, D1 and D2 based copolymers.

**Fig. 4** DSC analysis for DL16634, DL18020 and DL15050.

**Fig. 5** TEM micrographs of triblock copolymer (a) DL15050 in toluene, (b) DL16634 in toluene, (c) DL18020 in toluene and (d) DL15050 in chloroform.

**Fig. 6** SEM micrographs (a) salicylic acid loaded microsphere for DL16634, (b) surface of salicylic acid loaded microsphere before release, (c) surface of salicylic acid loaded microsphere after release and (d) pores generated on microsphere surface after release.

**Fig. 7** FTIR spectra of microsphere, salicylic acid loaded microsphere and salicylic acid.

**Fig. 8** Salicylic acid release profile from microsphere.

**Scheme 1** Sequential synthesis of D, L-lactide- δ-valerolactone- D, L-lactide triblock copolymer.

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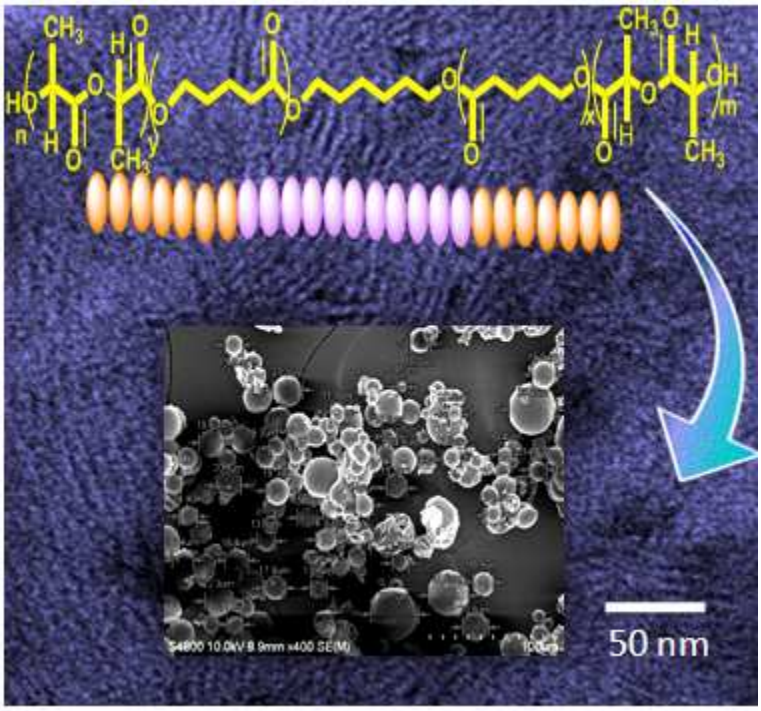



D, L-lactide - δ-valerolactone- D, L-lactide triblock, synthesized by sequential ring opening polymerization, exhibited nanolameller morphology and was fabricated into microsphere for drug delivery.

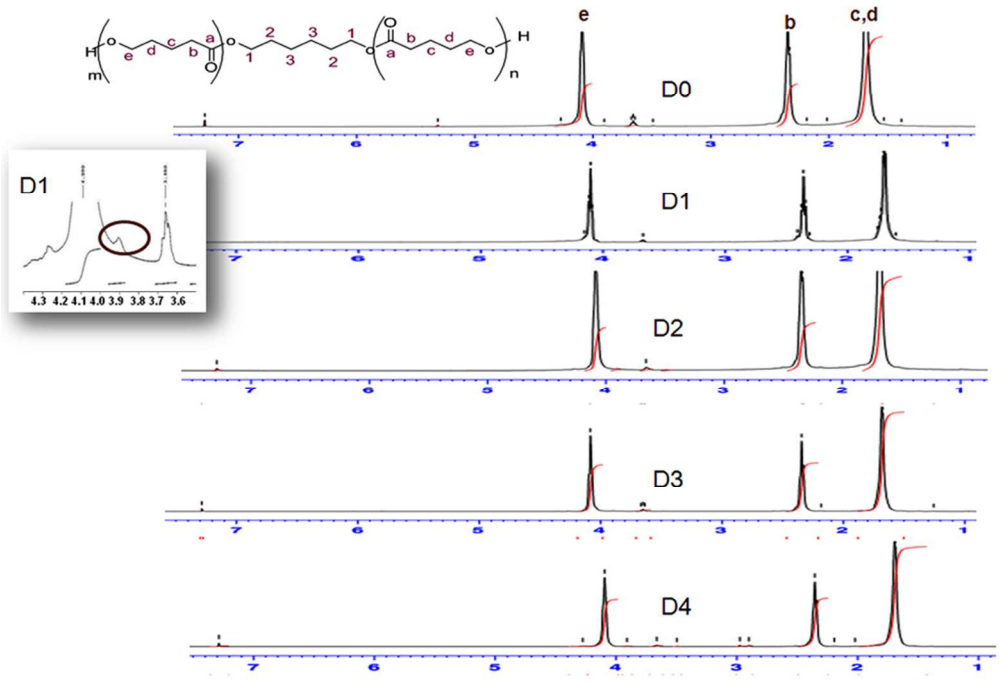



Fig. 1a 1H NMR Spectra of δ-valerolactone homopolymers D0, D1, D2, D3 and D4 and inset showing a small peak at 3.9ppm for D1.
88x61mm (300 x 300 DPI)

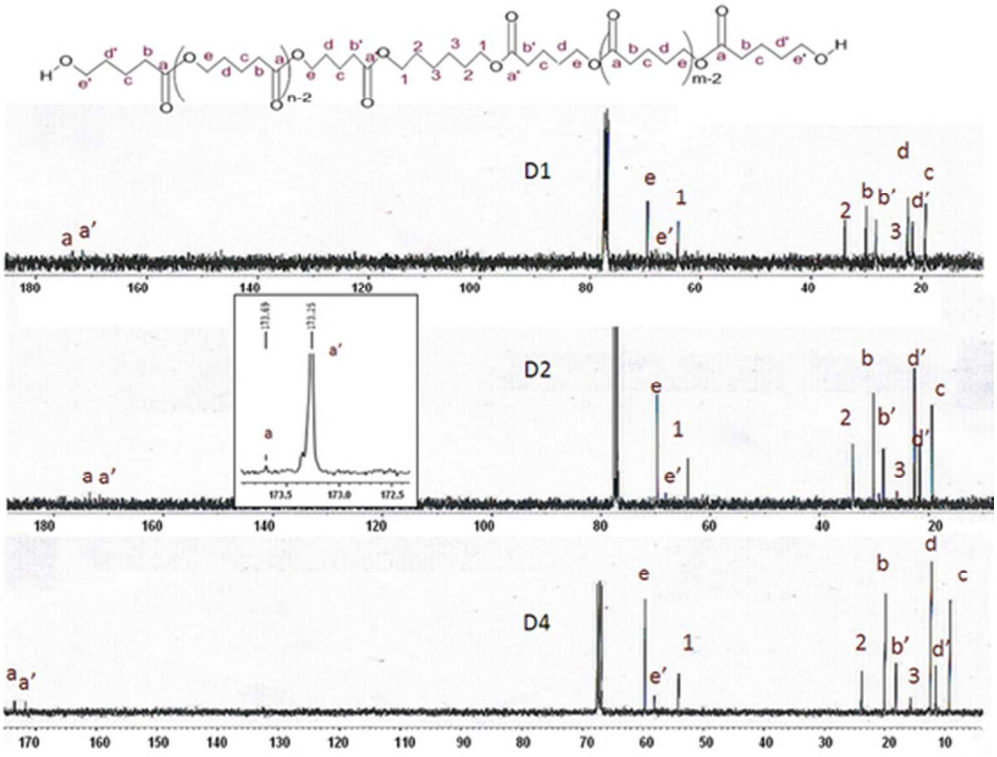



Fig. 1b 13C NMR Spectra of poly δ-valerolactone homopolymers D1, D2 and D4 and inset showing expanded carbonyl region for D1.
48x36mm (300 x 300 DPI)

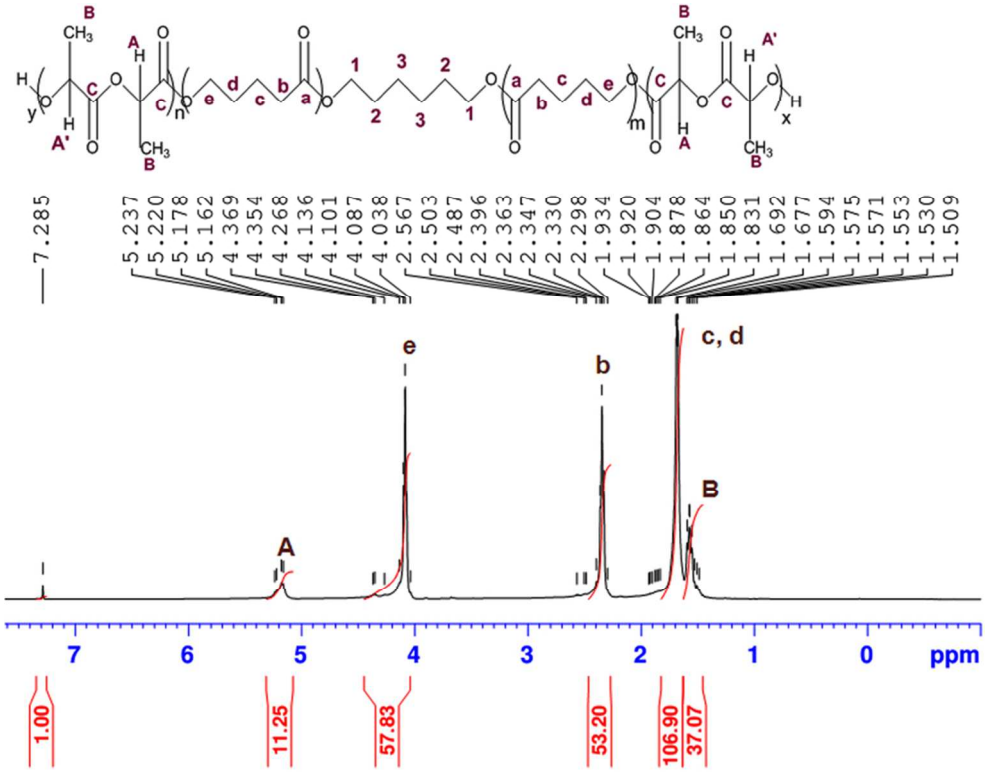



Fig. 2a 1H NMR Spectra of a representative copolymer, DL15050.
85x66mm (300 x 300 DPI)

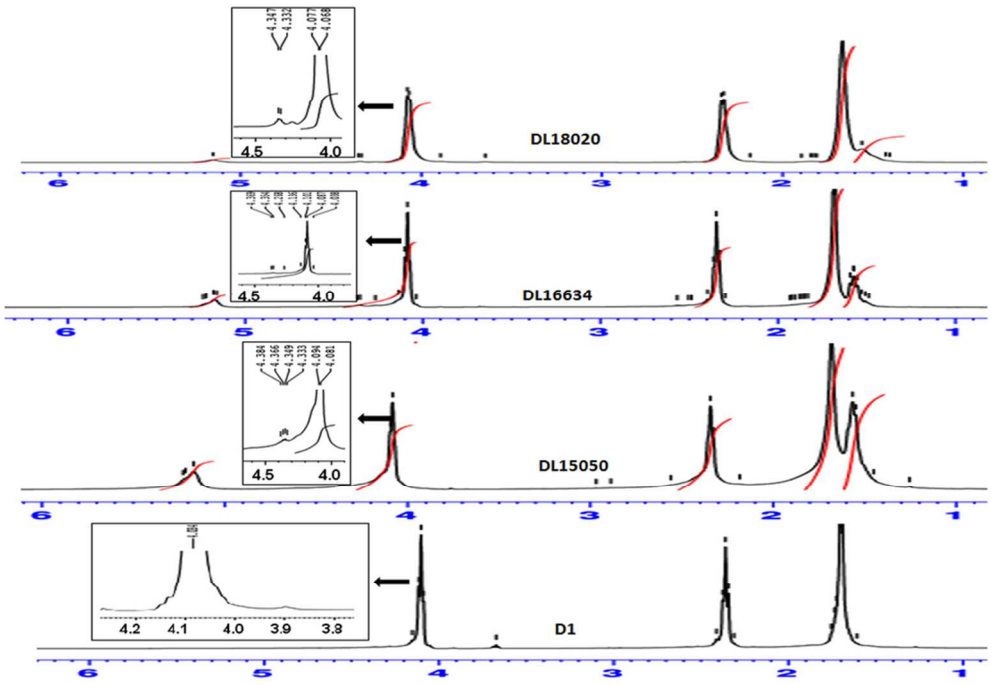



Fig. 2b 1H NMR spectrum of D1 showing signal around 3.9ppm and 1H NMR spectra for DL15050, DL16634, DL18020 showing signal around 4.3ppm in the expanded region.
87x59mm (300 x 300 DPI)

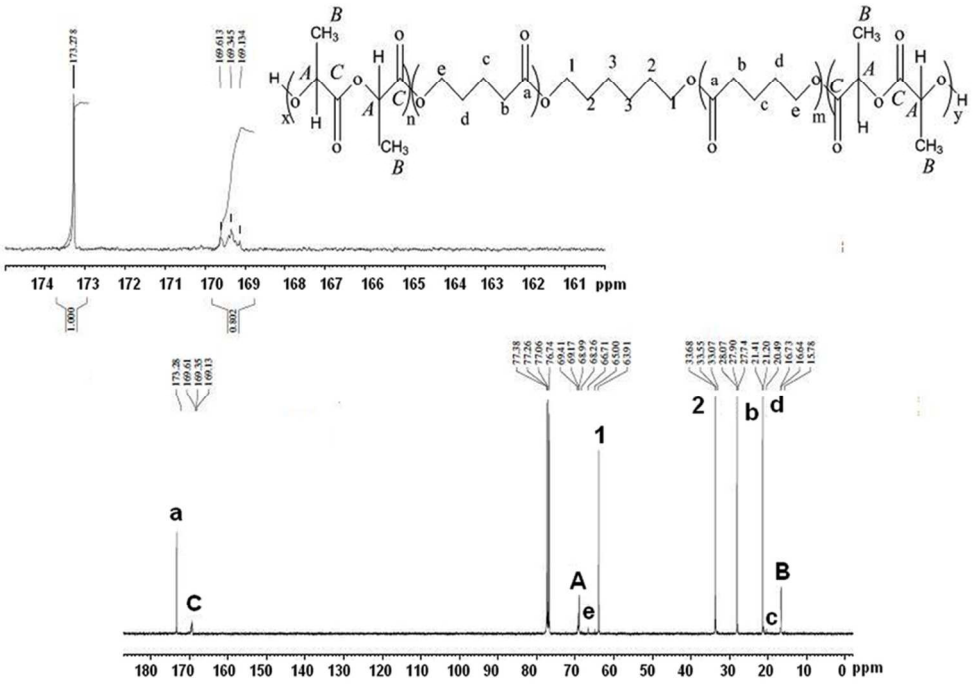



Fig. 2c 13C NMR Spectra of representative copolymer DL15050.

83x61mm (300 x 300 DPI)

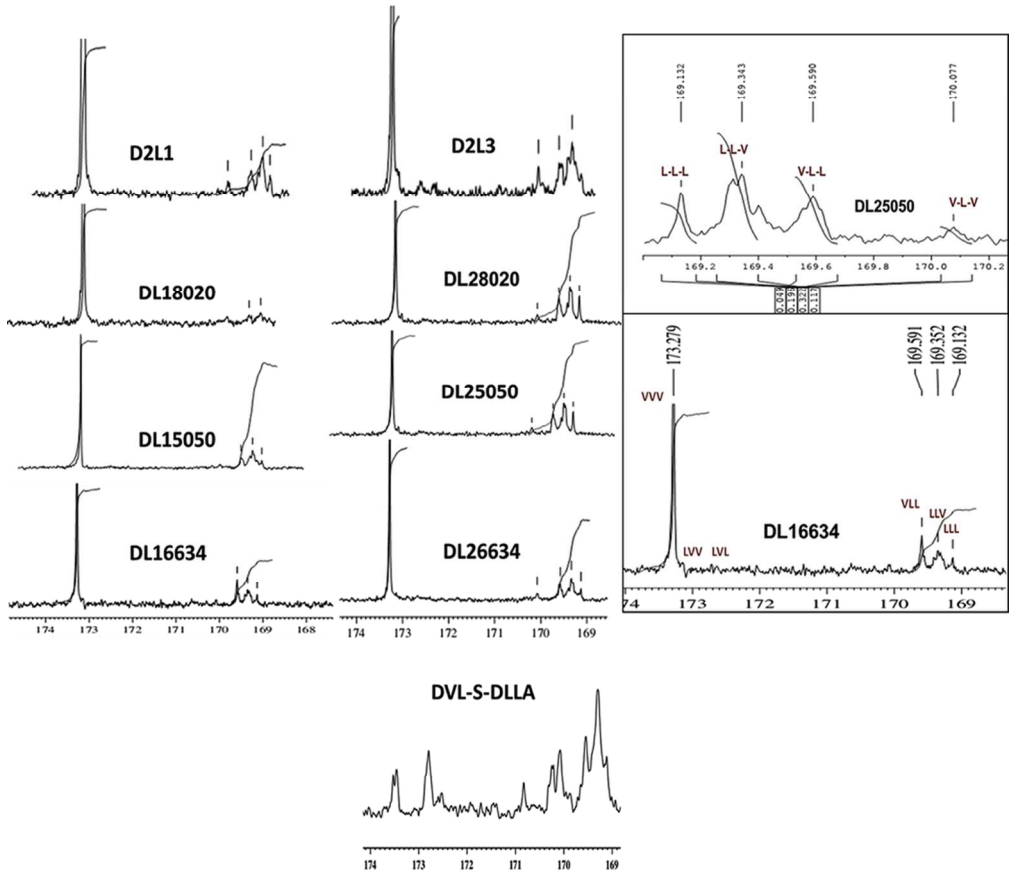



Fig. 2d 13C NMR spectra for copolymers showing the expanded C=O region (169-173 ppm).

121x106mm (300 x 300 DPI)

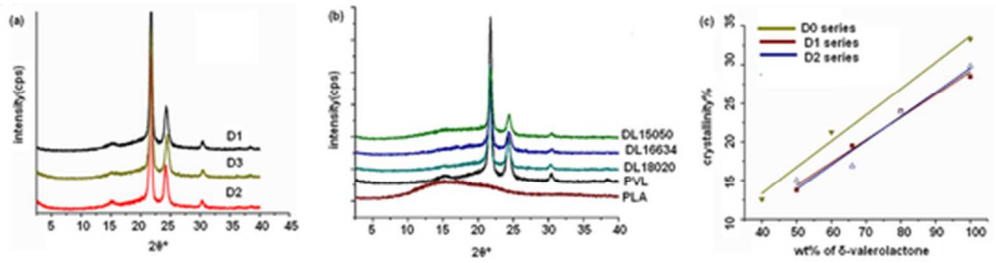



Fig. 3 (a)WAXD patterns for homopolymers D1, D2 and D3, (b) A comparison of WAXD patterns between homopolymer poly δ –valerolactone( PVL) and poly D, L- lactide ( PLA) and copolymers DL15050, DL16634, DL18020,(c) %crystallinity variation with increasing concentration of δ –valerolactone showing for D0, D1 and D2 based copolymers.

45x12mm (300 x 300 DPI)

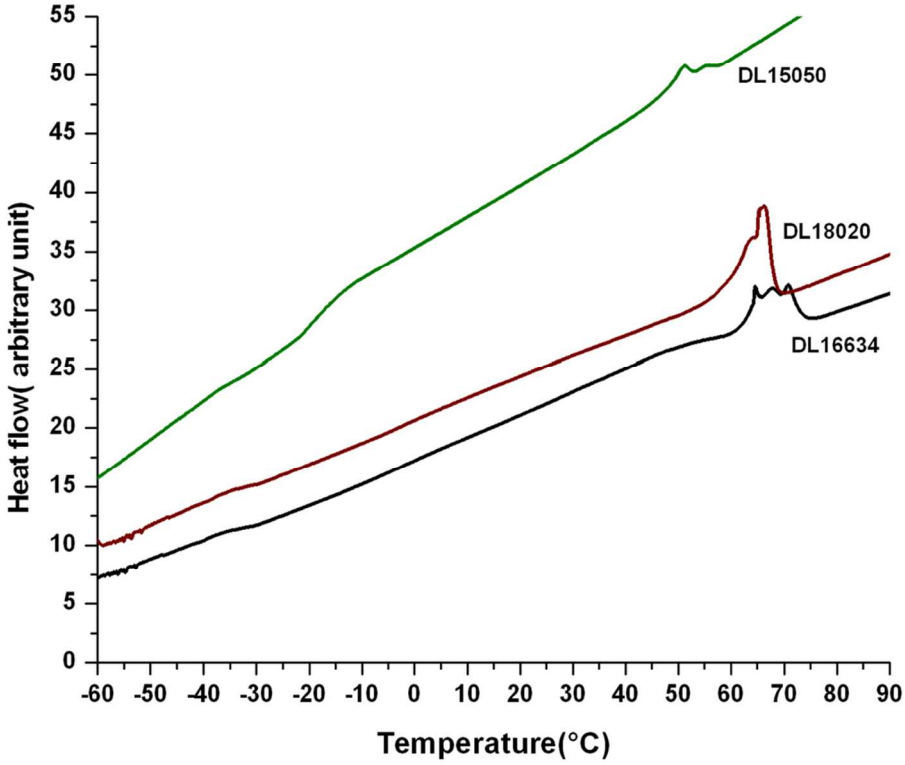



Fig 4. DSC analysis for DL16634, DL18020 and DL15050.
96x78mm (300 x 300 DPI)

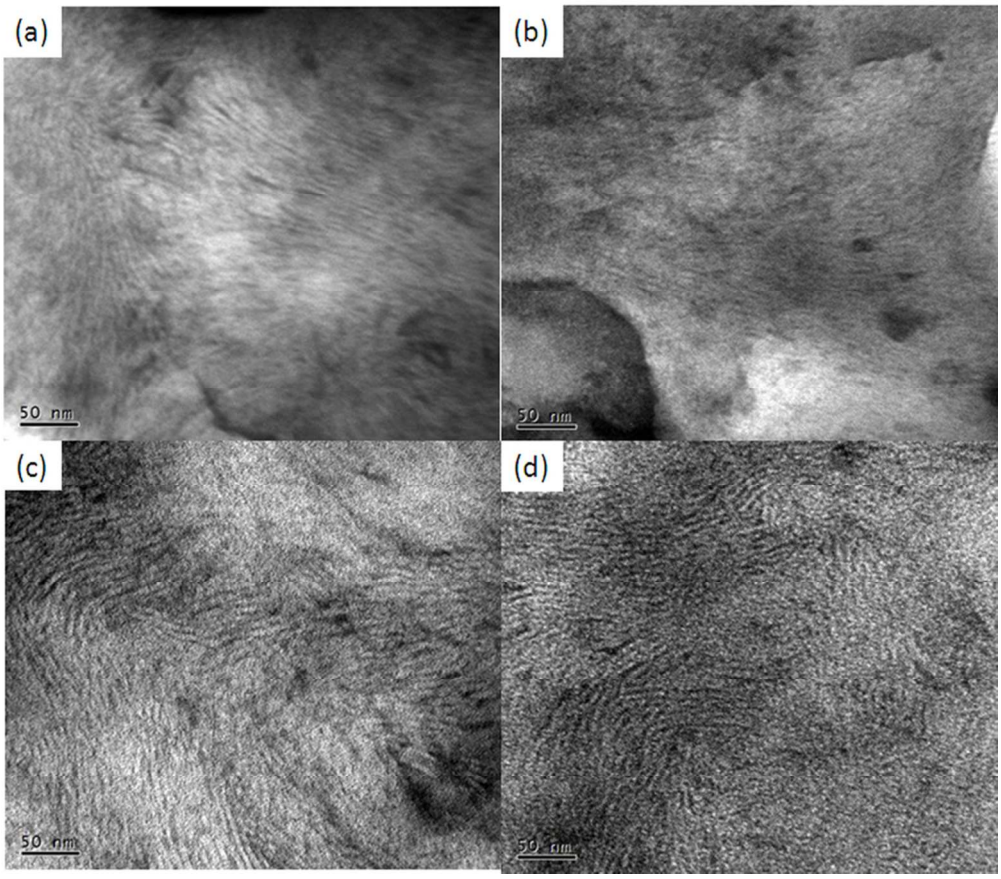



Fig. 5 TEM micrographs of triblock copolymer (a) DL15050 in toluene, (b) DL16634 in toluene, (c) DL18020 in toluene and (d) DL15050 in chloroform.
86x75mm (300 x 300 DPI)

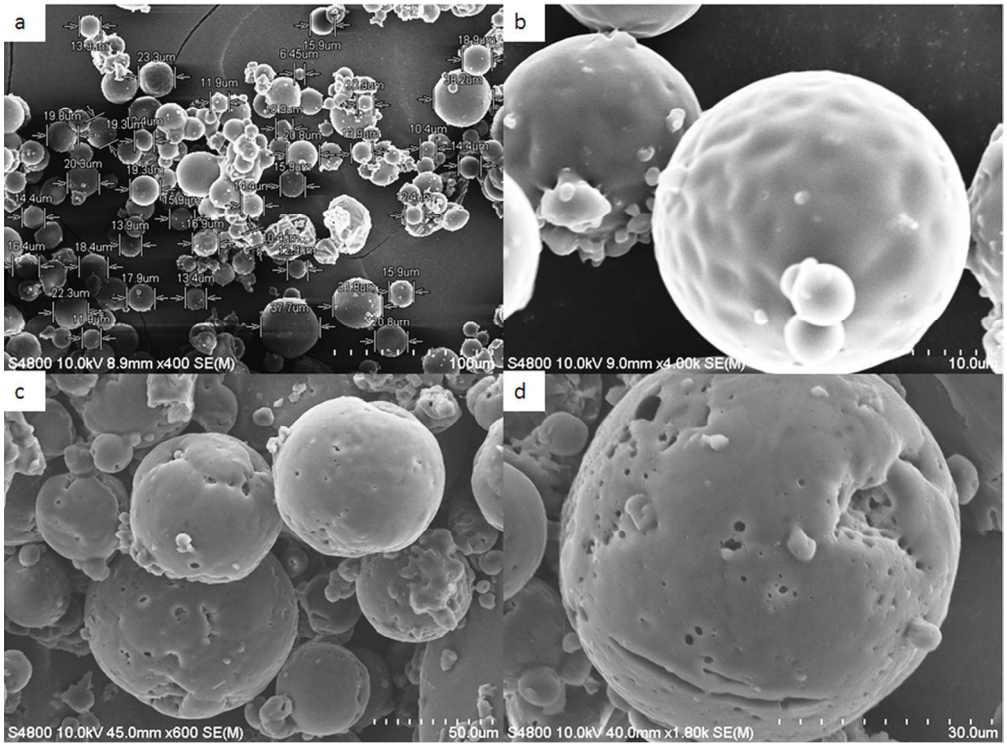



Fig. 6 SEM micrographs (a) salicylic acid loaded microsphere for DL16634, (b) surface of salicylic acid loaded microsphere before release, (c) surface of salicylic acid loaded microsphere after release and (d) pores generated on microsphere surface after release.
93x69mm (300 x 300 DPI)

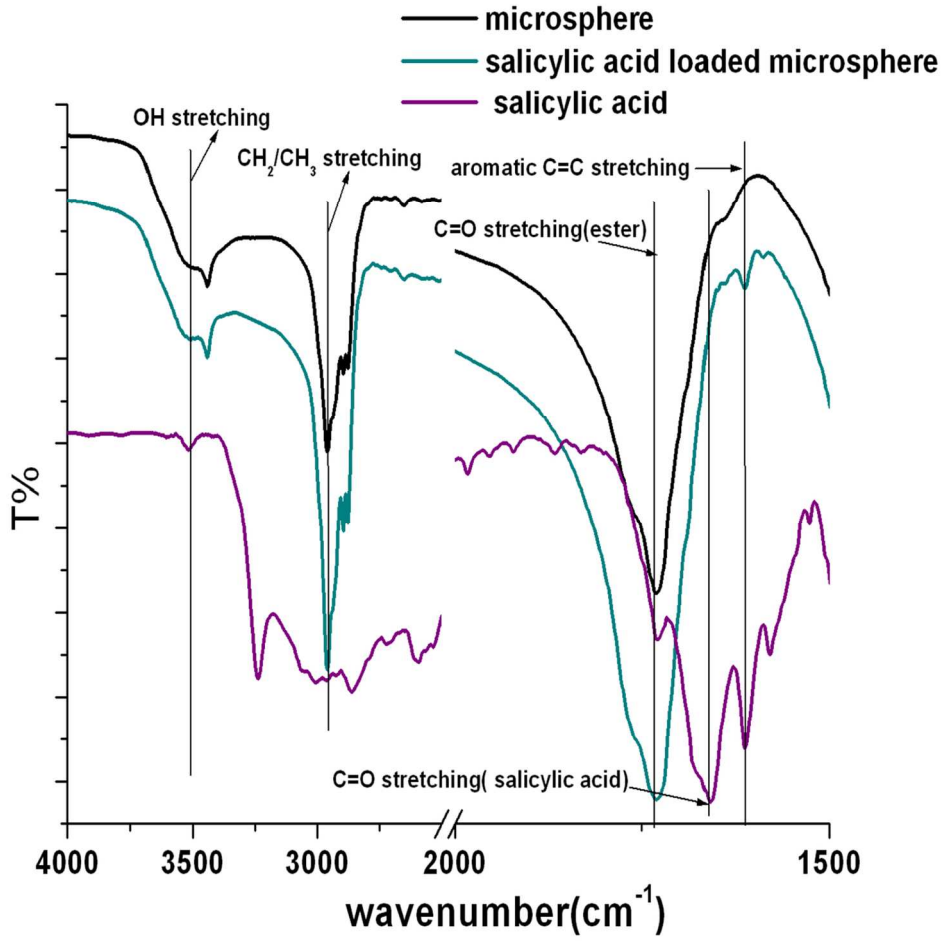



Fig. 7 FTIR spectra of microsphere, salicylic acid loaded microsphere and salicylic acid.
119x114mm (300 x 300 DPI)

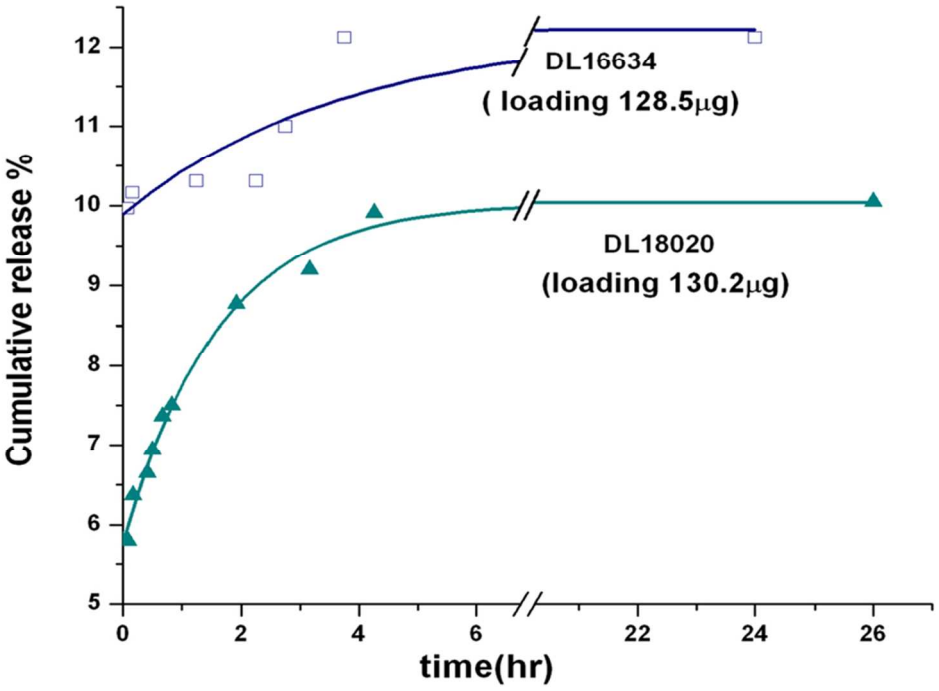
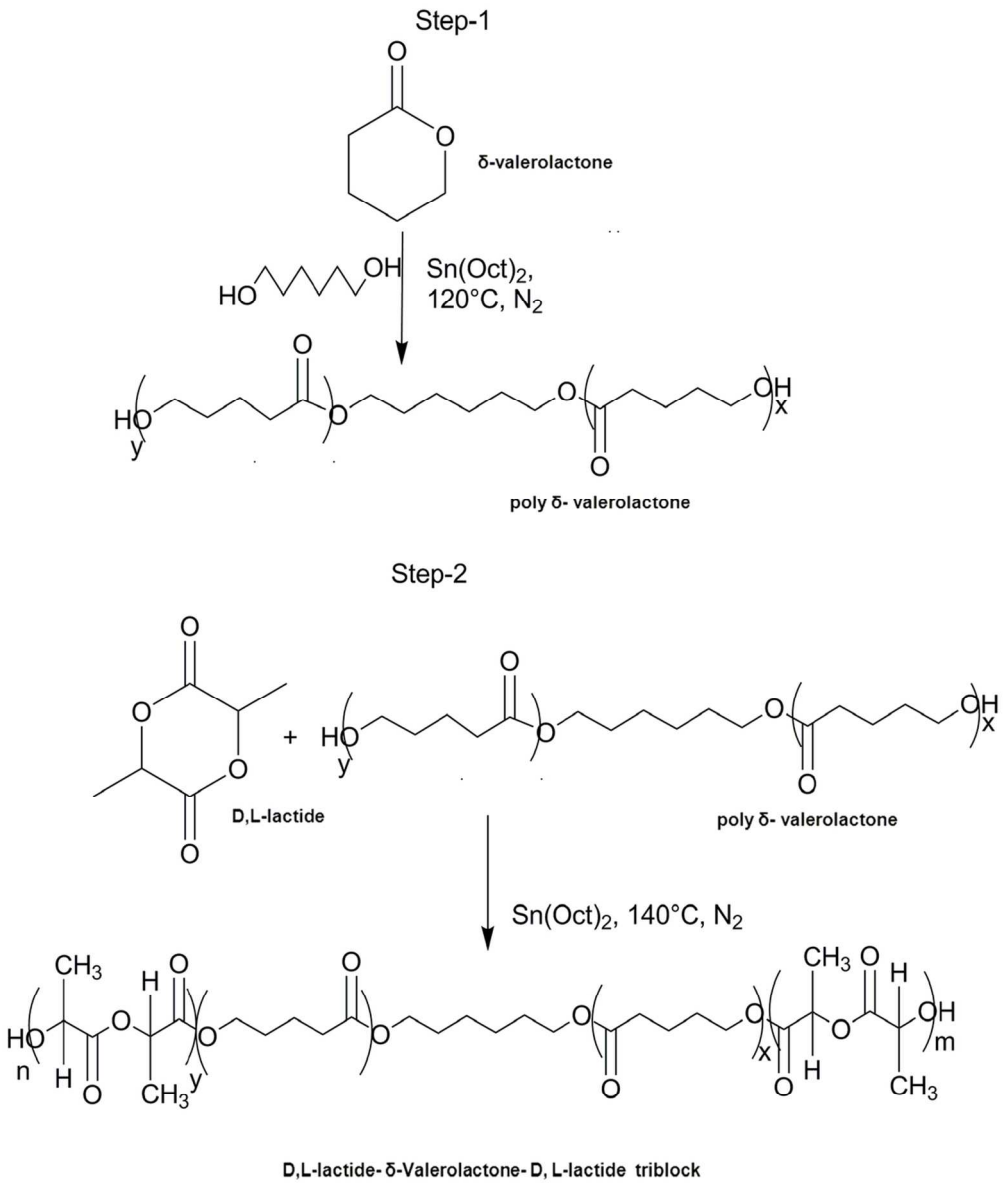



Fig. 8 Salicylic acid release profile from microsphere.
88x69mm (300 x 300 DPI)




Scheme 1 Sequential synthesis of D, L-lactide- δ-valerolactone- D, L-lactide triblock copolymer.
104x123mm (300 x 300 DPI)