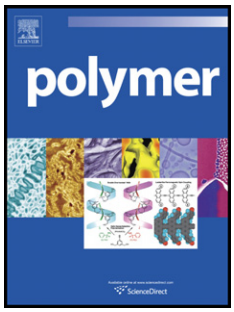
Accepted Manuscript



The contemporary role of #-caprolactone chemistry to create advanced polymer architectures

Adam L. Sisson, Duygu Ekinci, Andreas Lendlein

PII: S0032-3861(13)00392-3

DOI: 10.1016/j.polymer.2013.04.045

Reference: JPOL 16165

To appear in: *Polymer*

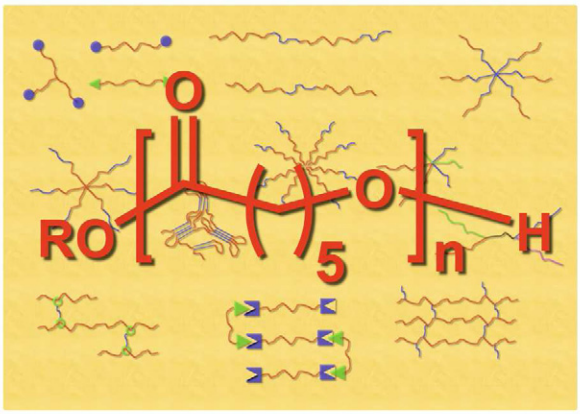
Received Date: 1 March 2013

Revised Date: 12 April 2013

Accepted Date: 14 April 2013

Please cite this article as: Sisson AL, Ekinci D, Lendlein A, The contemporary role of #-caprolactone chemistry to create advanced polymer architectures, *Polymer* (2013), doi: 10.1016/j.polymer.2013.04.045.

- Telechelic oligomers are described as building blocks for advanced architectures
- Multiblock and star-shaped copolymers as well as their potential applications are covered
- Supramolecular polymer systems based upon PCL are introduced as versatile materials
- Polymer networks containing PCL are highlighted for their stimuli-responsive behaviours
- PCL based particulate systems for controlled drug release are presented
- The role of PCL in shape-memory polymers as switching segment is explained



The contemporary role of ε-caprolactone chemistry to create advanced polymer architectures

Adam L. Sisson, Duygu Ekinci, and Andreas Lendlein*

Institute of Biomaterial Science and Berlin Brandenburg Centre for Regenerative Therapies, Helmholtz-Zentrum Geesthacht, Kantstrasse 55,14513 Teltow, Germany.

*****E-mail: andreas.lendlein@hzg.de

Phone: +49 (0) 3328 352 450

Fax: + 49 (0) 3328352 452

Abstract

Poly(ε-caprolactones) (PCLs) belong to the first generation of synthetic aliphatic polyesters. Their biodegradability motivated their extensive exploration as resorbable materials, particularly in controlled drug release applications. While PCL fell out of fashion due to the increasing popularity of shorter chain polyglycolides and derivatives, there has been a noticeable renewed interest in ε-caprolactone derived components for copolymer systems with advanced functions in the last decade or so. PCL has particular properties that are attractive for the design of tunable biomaterials such as slow crystallization kinetics and low melting temperatures in the physiological range. Slow degradation rates, with relatively minimal acid generation, can be valuable for prolonged drug release or longer-term stability of implants. Herein we cover recent developments of PCL chemistry, focussing on innovative uses of ε-caprolactone-based segments in sophisticated polymer architectures such as multiblock copolymers networks, and micellar systems. Such polymer constructs are of high interest for biomedical applications.

Keywords

Poly(ε-caprolactone), block copolymer, biodegradable, micelles, shape-memory effect, polymer network, precursor

1. Introduction

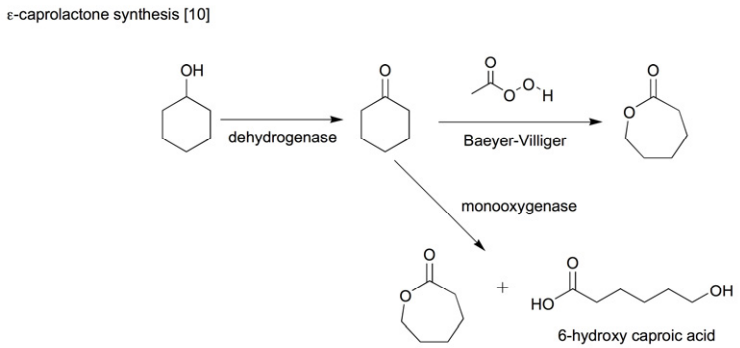
Poly(ε-caprolactone) (PCL) is one of the most important and widely studied degradable polymers with a history dating back to the very first synthetic polyesters in the 1930s. It is a saturated aliphatic polyester with hexanoate repeat units, and can be classed as semicrystalline with degrees of crystallinity up to 70% depending on weight average molecular weights (M_w)

typically ranging from 3,000 to 800,000 g·mol^{-1}. At higher molecular weights, crystallinity is reduced with increasing molecular weight - due to chain folding, such that at M_w = 200,000 g·mol^{-1}, 33% crystallinity is observed [1]. One of the first booms in interest in PCL came about when it was discovered that PCL materials could be completely degraded by bacterial and fungal enzymes making it of particular interest in biodegradable material applications. In addition to expected degradation by esterases, there is much evidence of PCL being susceptible to enzymatic degradation by lipase enzymes [2]. Degradation is possible within the body due to the ester bonds chemical lability towards hydrolysis, but the rate of ester hydrolysis under physiological conditions declines sharply as the number of chain carbon atoms increases. This became a factor in the movement away from PCL materials for degradable biomaterial applications; relative to the α-hydroxy alkanoates such as polyglycolides, PCLs degrade so slowly in the body it is difficult to gauge long term toxicities from degradation. PCL has a very low glass transition temperature and shows elastic behaviour at room temperature. In addition, relatively low melting temperatures, of around 60 °C, make PCL materials easy to fabricate or process into highly structured forms such as foams prepared in conjunction with super-critical CO_2 [3]. PCL is highly soluble in a range of non-polar solvents and is well known to be soluble with a wide range of other polymers for effective blending [4, 5].

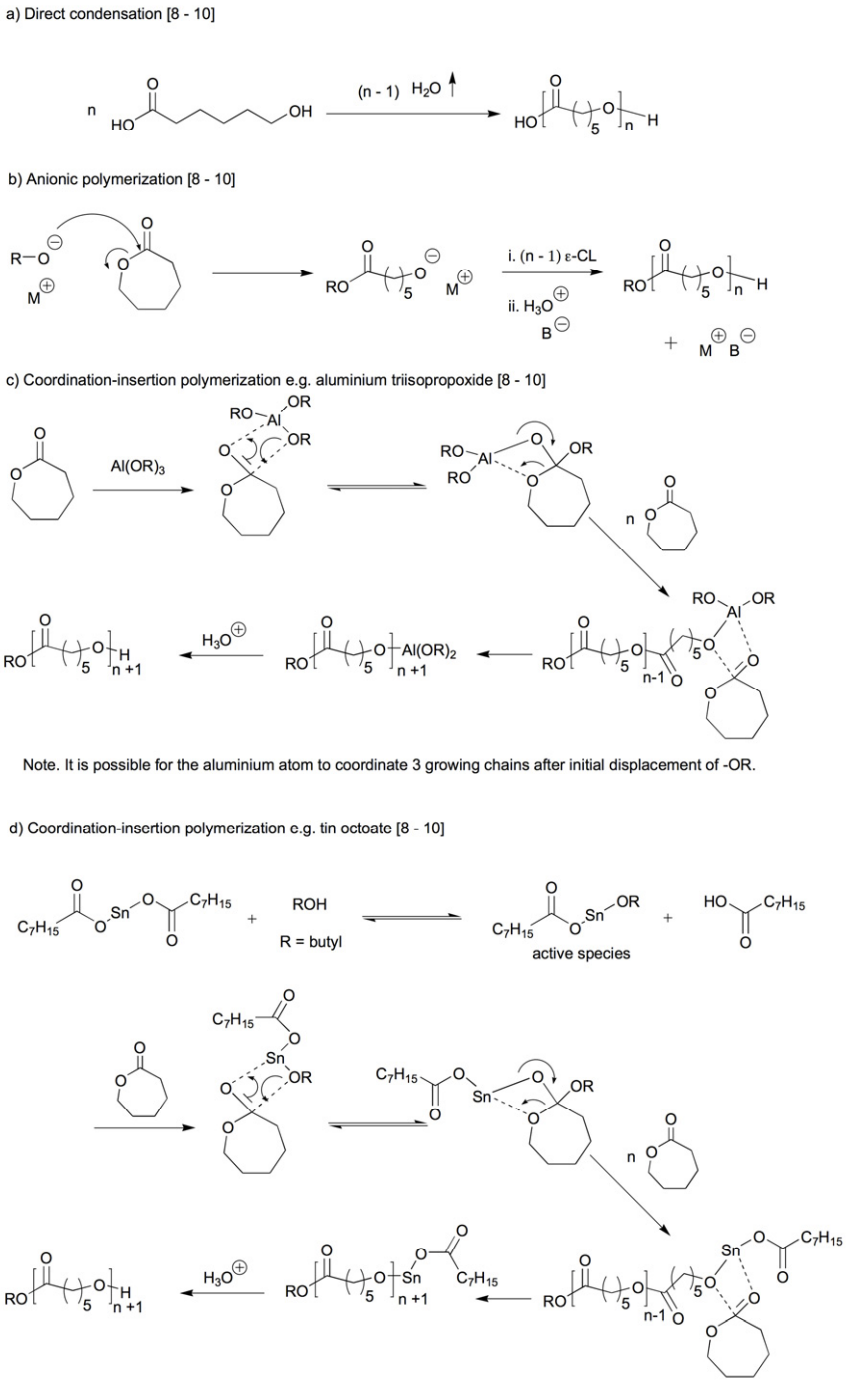
The degradation of PCL is complicated by the presence of distinct crystalline and amorphous domains, as access of water molecules into a bulk polymer are an important factor governing degradation rate in systems that undergo bulk hydrolyis. As water is able to diffuse in the amorphous regions of PCL, erosion does occur in bulk, as opposed to surface only. As has been observed in vivo, degradation occurs by an enzyme independent hydrolysis of exposed amorphous regions to liberate lower molecular weight crystalline fragments (M_w < 3000 g·mol^{-1}), which have been traced to intracellular degradation with the sole metabolite being 6-hydroxycaproic acid. Due to the more hydrophobic nature and less frequent ester linkages of PCL relative to polyglycolides, the release of acidic hydrolysis byproducts is reduced. This could cause less inflammatory responses in implant materials but the process is difficult to study and costly when considering that full degradation of PCL implants can take a number of years. Multiple studies point toward PCL-based materials having good biocompatibility. Despite reservations on the long term fate of PCL as a biomaterial, as covered in recent literature, there has been a marked upwards trend in investigations of such materials as particulate drug delivery vehicles, in cell cultivation, and in implants for regenerative

medicine and drug release [6]. In addition, the rheological properties of PCL have also been valuable to studying the very complex and poorly understood principles of polymer crystallization [7].

Although it is feasible to produce PCL by direct condensation of 6-hydroxycaproic acid, by far the most standard method for large scale synthesis of high molecular weight, low dispersity polymers, is via ring-opening polymerization of the 7 membered ring cyclic ester ε-caprolactone. Cyclohexanol can be oxidized by microorganisms to produce a mixture of ε-caprolactone and 6-hydroxycaproic acid. The most economical route to ε-caprolactone however comes from Baeyer-Villiger type oxidative ring expansions of cyclohexanone (Scheme 1). There are some reports of producing PCL with M_w up to 10,000 g·mol^{-1} by enzymatic means or by vigorously forcing removal of condensation byproducts to drive the equilibrium. The ROP polymerization chemistry of PCL largely mirrors that of other common lactones and dilactones such as glycolide and as such a large amount of research has been conducted in optimizing procedures. Anionic, cationic, and nonionic-nucleophile initiators can be used although problems with back-biting exist. Recent research seeks to utilize supramolecular interactions to enhance polymerization control by organocatalysis, or by using crown ethers to modulate counterion influences in anionic polymerization. Enzymatic methods are becoming more popular, screening lipase enzymes from various organisms. The method of choice though is to use a metal-based catalyst to polymerize ε-caprolactone by coordination-insertion mechanism [8, 9]. Metal complexes based around tin and aluminium are particularly effective at inhibiting backbiting and allowing very high M_w PCl (up to 800,000 g·mol^{-1}) with polydispersity approaching 1.1. These have certainly been used extensively in lactone ROP chemistry. Tin(II)octanoate and aluminium(III)isopropoxide are the most used catalysts but this is a rich field with much effort going into optimizing specific reactions and mechanisms, transition metal catalysts, and rare earth metal catalysts. Synthetic methods for PCL have been covered in more detail in recent reviews (Scheme 2) [10], including detailed mechanistic overviews [8, 9].



Scheme 1. Most common synthetic routes to ε-caprolactone monomers.



Scheme 2. Most common synthetic routes to PCL.

It is then clear that PCL is an ideal starting point for fabrication of synthetic materials for modern applications. In a quest to further tailor material properties towards specific aims, copolymers of PCL have been investigated for a range of comonomers by numerous synthetic methods [11]. In the fields of tissue engineering and drug delivery, PCL-based formulations as copolymers or as blends with synthetic or biopolymers have received particular attention

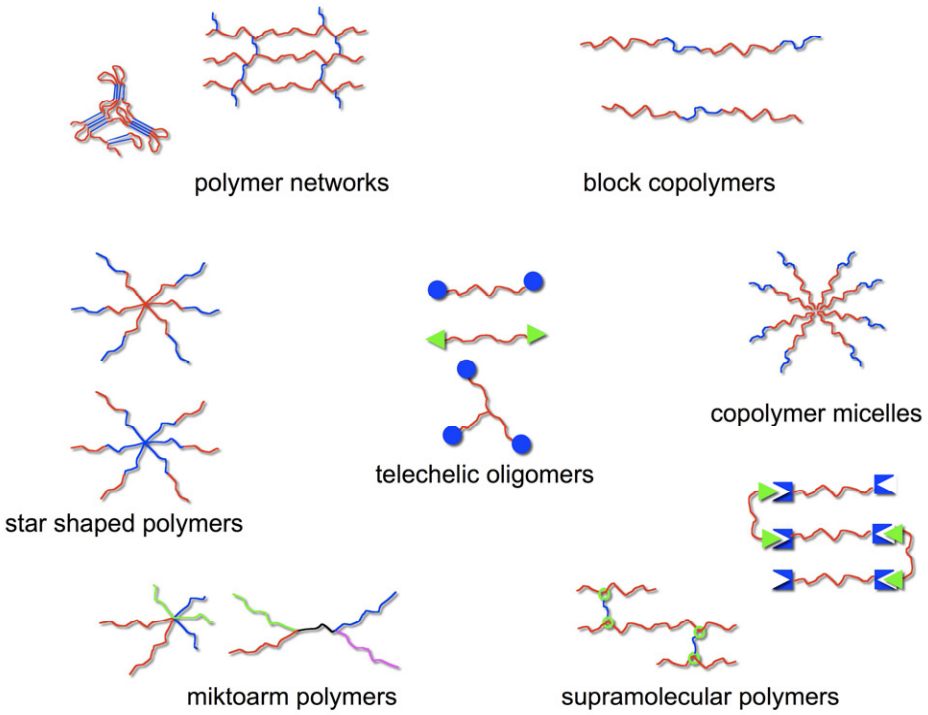
[12]. Of note, various investigations into di- and tri-component polyesters have been conducted in efforts towards combining the elasticity of PCL and the faster degradation times of the polyglycolides [13], or polycarbonates [14]. The material properties of copolymers such as PGLC (poly[glycolide-*co*-(L-lactide)-*co*-(ε-caprolactone)]) and PLC (poly[(L-lactide)-*co*-(ε-caprolactone)]) were investigated [15]. Introducing a relatively low proportion (< 10%) of caproyl units served to lower glass transition temperatures to below or around body temperature, which enabled use as drug releasing implant materials. Due to the obvious differences in reactivities (diglycolide > dilactide > ε-caprolactone) the abundance of homopolymer domains on PGLC chains are difficult to avoid and lead to higher than expected crystallinity. It was found that using $Zr(Acac)_4$ as catalyst gave more transesterification than the standard $Sn(Oct)_2$ which leads to more amorphous materials with more easily controlled degradation rates and thermal transition temperatures [16]. PGLC copolyesters with very defined sequences have been prepared by polymerizing distinct "segmers" of known composition [17]. This allowed for less ambiguous sequence analyses by NMR methods and insightful investigations into polymer sequence structure influence on thermal transitions.

2. Content of the review

Applications of PCL as a bulk material are numerous, and have been the subject of recent reviews [6, 12]. This work will focus on ε–caprolactone derived oligomeric components for building advanced polymer architectures (oligo(ε-caprolactone); OCL). Scheme 3 illustrates a selection of such architectures, which will be discussed in the following. It is in such areas that ε–caprolactone chemistry is attracting a great deal of interest. For the review structure, sections covering the following areas are described:

- Telechelic oligomers and endgroup functionalization
- Multiblock copolymers
- Supramolecular polymers
- Star-shaped and miktoarm polymers
- Polymer networks

Additionally, some discussion will be made of ε–caprolactone-based polymers for functional materials such as in drug delivery or as shape-memory polymers.



Scheme 3 Different advanced polymeric architectures employing PCL segments. PCL segments are represented by red polymer chains.

3. Recent advances in ε-caprolactone derived polymer architectures

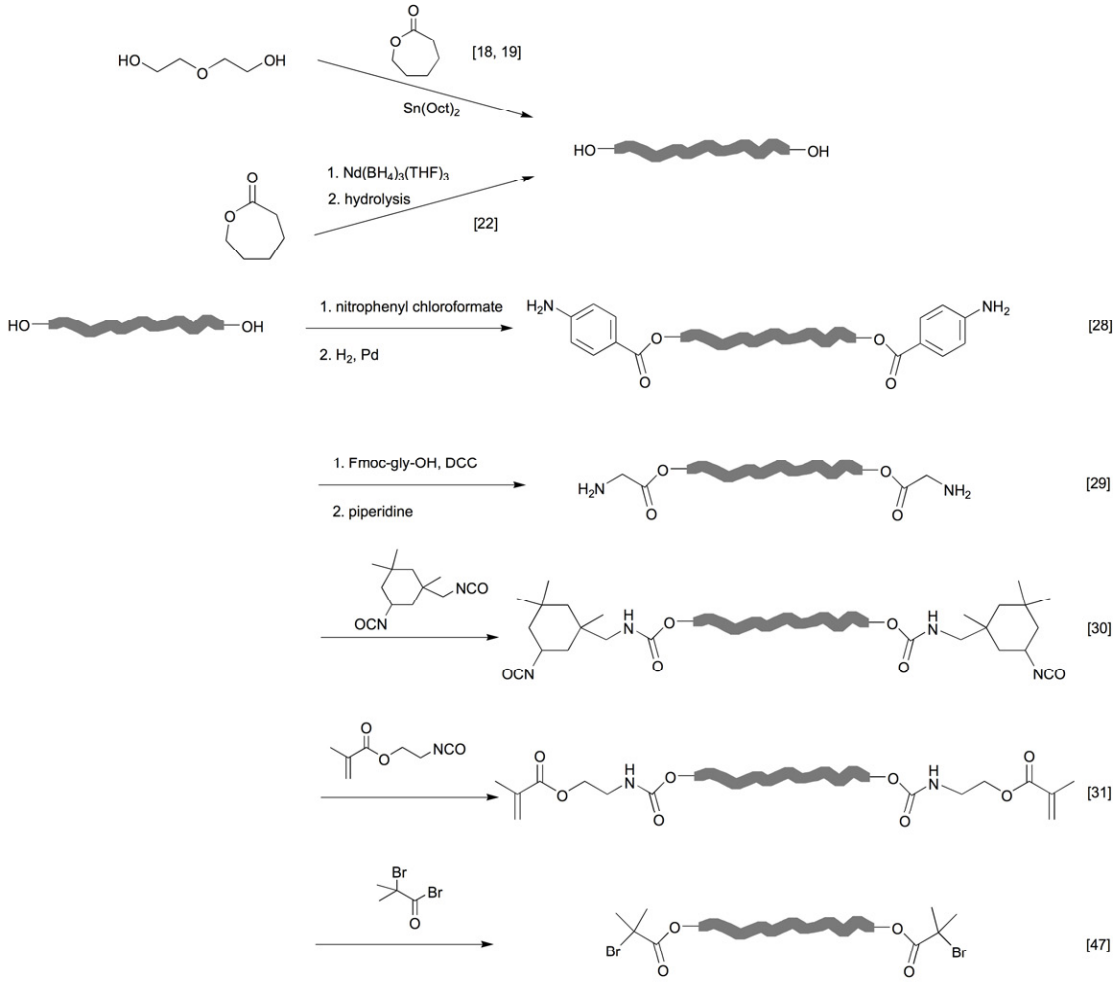
3.1 Telechelic oligomers and endgroup functionalization.

As an important note as to terminology, telechelic polymer diols may be sometimes more appropriately referred to as oligomer diols, as the free end groups play a significant role in the chemistry of the materials. The distinction should be made depending on the functional use of a telechelic segment, which is often dependent on the chain length. Shorter chains (average molecular weight approximately < 5,000 g·mol^{-1}), prepared as segments for multiblock copolymers may be termed as oligomers, although the distinction is not always made in literature. OCL diols, generally prepared by ε-caprolactone ring opening initiated by a low molecular weight diol [18, 19], are versatile telechelic segments with widespread uses in polyurethane chemistry [20]. It is also possible to prepare co-oligoester diols from diol initiators, by ring-opening polymerization of ε-caprolactone with cyclic diesters like diglycolides or other reactive lactones [21]. Depending on conditions employed, random, block, or statistical copolymer sequence structures can be prepared with tunable thermal properties and degradation profiles. In a study of copolymers of ε-caprolactone, diglycolide, and L,L-dilactide, there is a strong correlation between glass transition temperature varying from – 60 °C for OCL homopolymer diol and 40 °C for copolymer diols with high lactate

content. Melting temperatures of crystalline domains are also decreased in copolymers. However, above certain glycolate/lactate contents, only amorphous diols are formed and melting transitions are not observed. The degradation rate is increased by incorporation of the hydrolytically more labile ester bonds such as from α-hydroxy ester subunits. OCL diols can also be accessed directly by using a reductive initiator for ring opening such as $Nd(BH_4)_3(THF)_3$ [22]. An alternative route to ABA block copolymers with PCL as the central block follows the ring opening of caprolactone with a monovalent initiator such as poly(ethylene glycol) monomethyl ether (mPEG), and then subsequent condensation of mPEG-*b*-PCL terminal alcohols with a diisocyanate [23]. Multiblock copolymers can be prepared by condensation of PCL-diol with PEG-bis-chloroformate with molecular weights as high as 100,000 $g \cdot mol^{-1}$ achievable [24]. OCL diol macromonomers have also been crosslinked as silylethers by a palladium catalyzed dehydro cross-coupling reaction with a bis-silylbenzene [25]. The resulting materials had stepwise degradation profiles due to the relatively labile silylether bond. Chain extension of OCL diol and PEG using fumaryl chloride leads to a variety of multiblock copolymers which can be crosslinked photochemically to produce promising materials for tissue engineering applications [26]. Novel procedures have also been developed to functionalize OCL with electrophiles such as benzaldehyde and naphthoylchloride after deprotonation with lithium diisopropylamide [27].

OCL-based telechelics with a range of functional end groups are accessible from the parent alcohol (Scheme 4). Condensation of OCL diol with nitrophenylchloroformate and subsequent reduction gives an amino terminated telechelic macromolecule which can be extended by ring-opening polymerization with various amino acid *N*-carboxyanhydrides to give ABA polypeptide triblocks with an OCL core [28]. An alternative route to diamino telechelic PCL is the esterification of the terminal hydroxyl groups with protected glycine and subsequent deprotection [29]. A less conventional access to diamino OCL is possible via capping OCL terminal diols with isophorone diisocyanate via carbamate linkage [30]. Under the correct conditions only one isocyanate of isophorone reacts, resulting in an isocyanato functionalized telechelic. Hydrolysis of the remaining isocyanate groups gives the free amines which were used to form ABA triblock polymers of polycaprolactam and OCL. Polypeptide triblocks were again produced via this method as novel biomaterial candidates. Methacrylate groups have been appended to OCL diol by reaction with isocyanatoethyl methacrylate; the resulting telechelics could be photocrosslinked [31]. Nitroxide mediated radical

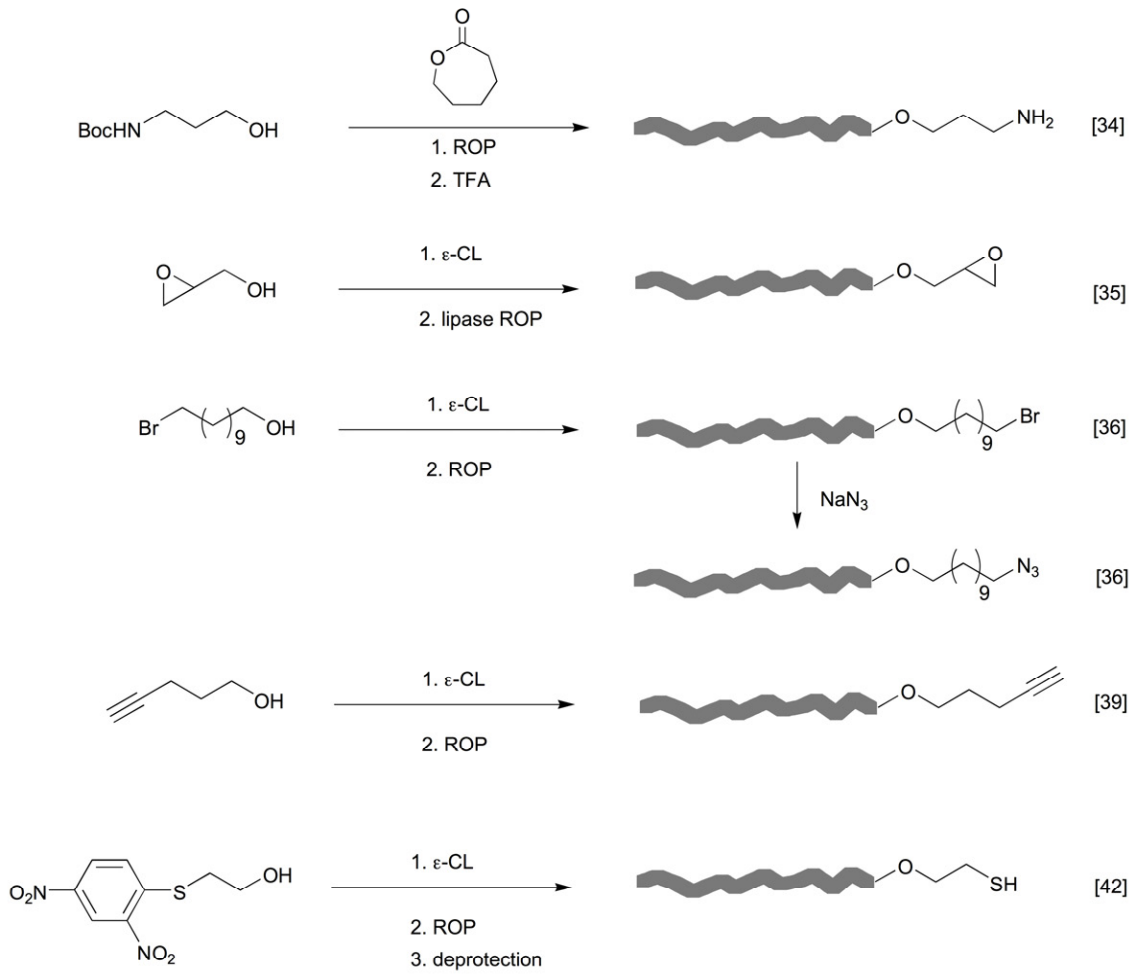
polymerization of OCL diacrylate with hydroxymethyl methacrylate (HEMA) was used to produce the triblock poly(HEMA-*b*-CL-*b*-HEMA) in a controlled fashion [32].



Scheme 4 Synthetic routes to PCL-based telechelics.

Monofunctional PCL initiated by aluminium isopropoxide was end group functionalized by quantitative esterification of the terminal alcohol with benzyl carbamate (Z) protected glycine or 6-aminohexanoic acid [33]. After Z deprotection the resulting PCL amine group was reactive towards various electrophiles. Alternatively, direct initiation of ε-caprolactone ROP with *t*-butyl carbamate (Boc) protected aminopropanol catalyzed by $ZnEt_2$ successfully led after deprotection to amino functionalized PCL, which was used to prepare poly[(ε-caprolactone)-*b*-glutamate] amphiphilic polyester-polypeptide (Scheme 5) [34]. These block copolymers were able to aggregate to form micelles with implications for controlled release applications. Epoxy functionalized PCL could be formed by initiation with glycidol catalyzed

by lipase [35]. The subsequent monoglycidyl PCLs were esterified through the terminal hydroxyl group with succinic anhydride and the resulting carboxylic acids could react with the epoxy groups at elevated temperatures, yielding branched structures. PCL azide can be produced by ROP initiated by ethylaluminium 12-bromo-1-dodecanol with subsequent nucleophilic displacement of bromide with sodium azide.[36] Grafting of PCL chains onto buckminsterfullerenes has been achieved via this method, leading to photoactive nanohybrid materials when electrospun into fibres with PEG-*b*-PCl copolymers. A related method of grafting PCL chains onto buckminsterfullerenes proceeded via the PCL amine derived from the aforementioned azide by hydrogenation [37]. PCL can also be esterified with pentynoic acid containing an alkyne group which is a versatile substrate for copper catalyzed “click” cycloaddition to azides [38]. Alternatively, alkyne bearing PCL can be prepared by ROP initiated by 4-pentyne-1-ol in the presence of a rare earth catalyst at low temperature [39]. Intricate star shaped block copolymer architectures have been formed using click conjugation [40, 41]. The preparation of thiol functionalized PCL is also possible through either initiation of ROP by a protected thiol-containing alcohol, or by appending a protected thiol group to PCL alcohol by esterification [42]; more recently, these transformations have been performed without needing thiol protection by using a lipase enzyme [43].



Scheme 5 Methods to introduce reactive functionality to PCL terminus.

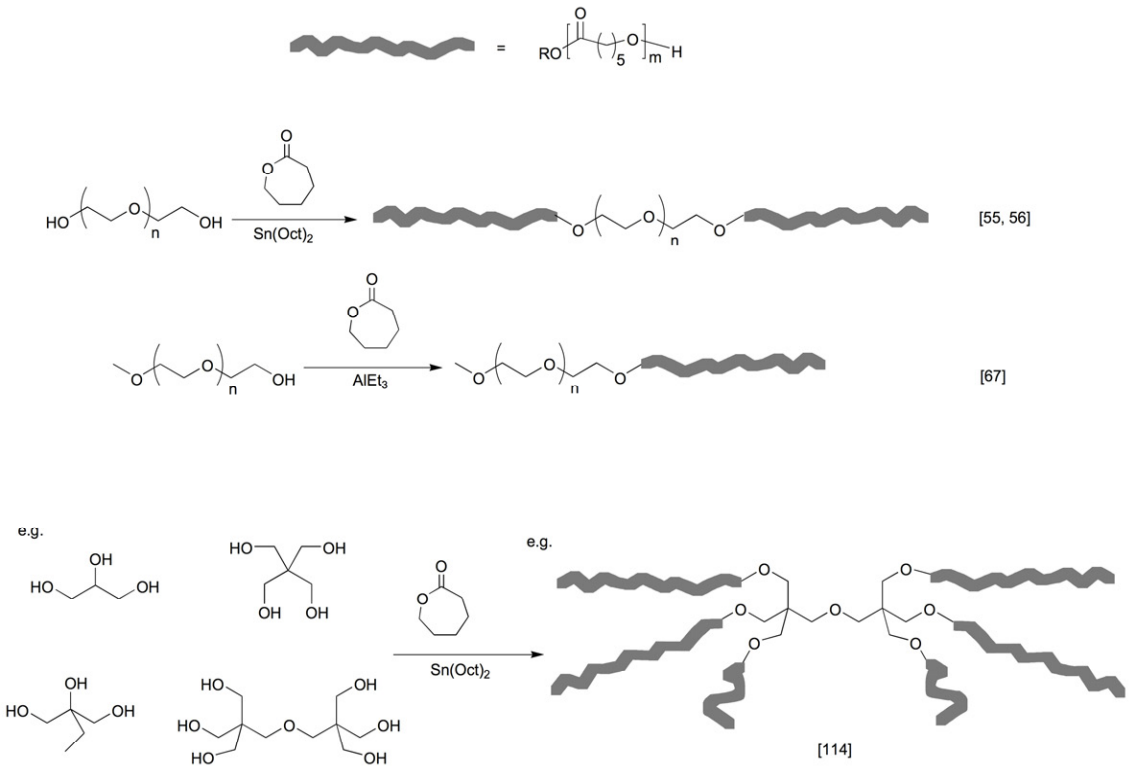
Methods to introduce chain ends with living polymerization initiators have been developed [44-46]. Conversion of the terminal PCL alcohol to a methyl methacrylate ester provides a substrate which undergoes ATRP copolymerization with dimethylamino methacrylate (DMEAMA) to afford the graft copolymer poly(DMEAMA-*g*-CL) [47]. In the same study, aiming towards amphiphilic copolymers, PCL esterified with bromobutyric acid was used as macroinitiator for ATRP to produce the block copolymer poly(CL-*b*-DMEAMA). Much recent attention on living polymerizations has focussed on the synthesis of exotic star polymer architectures. In early work, star-shaped PCL was endgroup functionalized with bromobutyrate containing dendrons which served as a macroinitiator for the ATRP of various methacrylate monomomers or comonomers leading to a range of block copolymers with very narrow polydispersity [48]. Nanoaggregate-forming triblock copolymer amphiphiles have been prepared using this methodology based around PCL stars grown from a hyperbranched

poly(2-hydroxyethyl methacrylate) core; an outer shell of 2-polydimethylaminoethyl methacrylate or poly-*t*-butyl methacrylate was appended by ATRP [49]. Unimolecular micelles have been prepared by appending a dense poly(ethylene glycol) methacrylate shell to a hydrophobic star shaped PCL core by ATRP [50]. The method is proposed as a straightforward alternative to standard PEGylation techniques which may require prohibitive reaction conditions. This chemistry has been extended to include the polymerization of styrene derivatives [51, 52]. Hydrophilic methacrylamide shells have been added to PCL cores with thiol end groups by free radical polymerization of *N*-(2-hydroxypropyl)methacrylamide [53].

3.2. Multiblock copolymers

3.2.1 Synthetic block copolymers

Amphilic block copolymers of PEG and PCL were introduced in the 1970s and since attracted considerable attention (Scheme 6) [54]. PCL-*b*-PEG-*b*-PCL triblock copolymers prepared by standard ring-opening polymerization of poly(ethylene glycol) show interesting thermosensitive sol-gel behaviour in aqueous solution [55, 56]. Studies reveal that such transitions are dependent on block lengths and are governed largely by the crystallization kinetics of PCL [57]. Such behaviour is based upon the microphase separation of such polymers and is closely related to their heavily studied micellization. Hydrophobic drugs can be loaded within PCL-*b*-PEG-*b*-PCL micelles with potential for controlled release [58]. Such polymeric micelles showed minimal in vitro toxicity and were hemocompatible; cellular uptake was found to depend on polymer architecture in a comparison between triblock polymers and corresponding amphiphilic star polymers [59]. A more controlled synthesis of the ABA triblock copolymer has been developed via ring opening polymerization of ε-caprolactone with a macrocylic tin-alkoxide PEG initiatior. The resulting telechelics were used as components of drug releasing polymer networks [60]. With regards to studying tissue engineering aspects, it has been shown that PEG-*b*-PCL diblock and ABA copolymers degrade more rapidly than the PCL homopolymer due to an increased hydrophilicity and water uptake in PBS buffer [61]. However, there is evidence that PEG blocks have less effect on enzymatic degradation rates of PEG-PCL block copolymers [62].



Scheme 6 Linear (section 3.2.1) and star shaped (section 3.4.1) architectures derived by ROP.

Ring opening polymerization initiated by monofunctional methyl poly(ethylene glycol) (mPEG) leads to diblock copolymers which have been extensively studied in micellar systems. In a series of studies, lower molecular weight amphiphiles such as $mPEG_{17}$-*b*-PCL_5 have been found to influence cell membrane fluidity and effect membrane proteins relevent to drug uptake and bioavailability pathways [63, 64]. There is evidence that these copolymers can inhibit the expression of certain glycoproteins, thus suppressing multidrug resistance in cancer cells [65]. mPEG-*b*-(PCL-*ran*-PLLA) copolymers have been investigated as injectable in situ forming gels [66]. These copolymers undergo sol-gel transitions around body temperature and degrade over a much longer timescale than poly(α-hydroxyalkanoate) copolymers such as mPEG-*b*-PLLA. Small amounts of PLLA (< 10%) were incorporated in the polyester chain to allow for controlled degradation times. Gelation and immunogenicity tests were conducted in vivo with favourable results. The surface active propertites of mPEG-*b*-PCL were studied at the chloroform/water interface and compared to the novel amphiphilic graft copolymer PCL-*g*-PEG [67]. Interestingly, the graft copolymers at similar compositions had comparable surface activity. These PCL-*g*-PEG surfactants were evaluated as “stealth” conferring stabilizers of hydrophilic PLLA nanoparticles with consequent reduction of serum

protein adhesion in vitro [68]. Star shaped amphiphilic A_2B copolymers $(PCL)_2$-*b*-PEG can be synthesised by ring opening polymerization of ε-caprolactone onto an end modified mPEG diol [69].

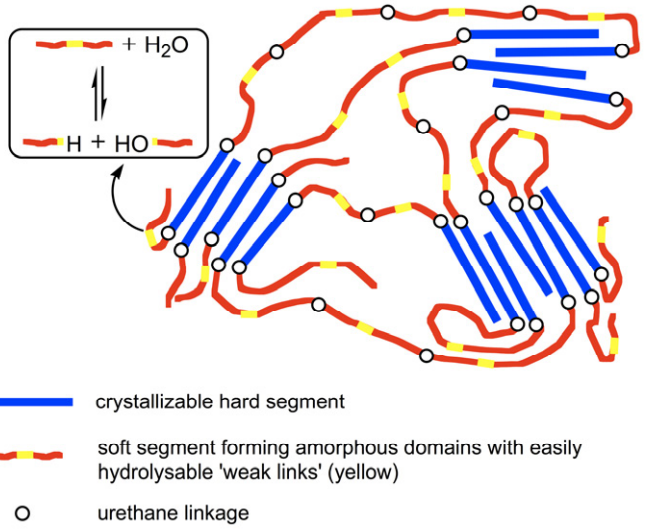
Block copolymers of PCL and PLLA are difficult to handle due to phase separation of both crystalline hydrophobic regions creating a brittle material with unfavourable properties. An interesting approach to circumvent this was reported by forming polymer chain inclusion complexes with α-cyclodextrins prior to polymer coalescence, with subsequent degradation of the cyclodextrins from the final material [70]. A relatively low crystalline product resulted which had dramatic influence on enzymatic degradation rates; PCL-*b*-PLLA formed via inclusion complexation degraded more rapidly than standardly produced diblocks of similar composition as a result of the abundance of the amorphous phase [71].

3.2.2 Polyesterurethanes

There has been a lot of interest in fabricating thermoplastic elastomers based upon segmented polyesterurethanes (PEU) with soft segments based on PCL-diol and oligourethane hard segments obtained from diisocyanate extended by a low molecular weight diol [20, 72]. The urethane groups are responsible for physical crosslinking through hydrogen bonds, and material properties can be readily controlled by hard segment content [73, 74]. Such polymer networks were investigated for applications in tissue engineering at an early stage; various aromatic and aliphatic diisocyanates with different chain extenders could be incorporated [75].

Highly tunable multiblock copolymer system with adjustable degradation behaviour and mechanical properties were obtained by co-condensation of poly[(3-*R*-hydroxybutyrate)-*co*-(3-*R*-hydroxyvalearate)]-diols and poly[(ε-caprolactone)-*co*-glycolide] diols with low molecular weight diisocyanate as junction unit. The avearge molecular weights of the telechelic diols ranged from around 500 to 3,000 $g \cdot mol^{-1}$ [76] (Scheme 7). The mechanical properties of such multiblock copolymers are governed by the weight content of the crystallizable poly(hydroxy butyrate) hard segments. The presence of glycolide units in the soft segments could increase degradation rate. The ester bonds between two glycolide units are the most easily hydrolysable links in the final architecture and are therefore named `weak links´. In this way the elastic properties and degradation rate could be controlled almost independently from each other. Low molecular weight diols conjugated with a fluorescent

dansyl-based moiety could be incorporated into such PEU systems in order to study degradation behaviour relevant to biomedical applications [77]. This also serves as a proof of principle that other moieties, for instance bioactive compounds, could be incorporated into such materials and subsequently released through degradation. A PEU system derived from soft oligo(*ε*-caprolactone) segments and hard oligo(p-dioxanone) segments was reported as a degradable shape-memory polymer, suitable for medical devices that undergo a change in shape upon implantation [78]. As described in more detail in Section 4.3, the crystalline PCL-segments are able to form physical netpoints to stabilize a second temporary shape. Melting of PCL domains induces the recovery of the original permanent shape (shape-memory effect). As a further example of a PEU with interesting thermal properties, PCL and poly(*ω*-pentadecalactone) (PPDL) could be condensed to form 'temperature-memory' materials which can be deformed at a given temperature T_{deform}, then set in that geometry by cooling. Upon reheating the deformation is recovered once the T_{deform} is exceeded [79]. PCL and PPDL are both crystallizable. The melting temperatures associated to the crystalline domains can be adjusted by varying the molecular weight of the macrodiols in the starting material mixture of the synthesis. These parameters, along with co-macrodiol ratio, could be varied to give materials thermoresponsive in the range of 30 – 60 °C, and applications as temperature-memory catheters with shape shifting capabilities were demonstrated.



Scheme 7 Multiblock copolymer thermoplastic architecture, with crystallisable poly[(3-*R*-hydroxybutyrate)-*co*-(3-*R*-hydroxyvalearate)] hard segments and poly[(*ε*-caprolactone)-*co*-glycolide] soft segments containing easily hydrolysable ester bonds.

Material hydrophilicity can be controlled by incorporating PEG-diols or pluronic PEG-*b*-PPG-*b*-PEG-diols alongside PCL-diol in variable ratios [80]. This has implications in controlling degradation rates with generally the more hydrophilic networks undergoing more rapid mass loss [81]. Detailed studies on the relationships of various chain extenders and bis-isocyantes and mechanical properties, degradation rates, and cytotoxicity have been performed [82]. Highly biocompatible materials can be produced and studies show fibroblasts proliferating well on material surfaces with no disturbance to morphology. PCL-based PEUs can be blended with natural-based biopolymers such as plasticized starch where the hydrogen bonding interactions between urethane groups and starch hydroxyl groups can be manipulated to greatly increase the mechanical properties of the starch blend and control degradation rates [83]. Such materials are of great potential interest as biodegradable materials owing to the abundance of starch [84].

Stimuli-sensitive polyurethanes may be prepared by using a functional chain extender such as the carboxylic acid containing diol bicine [85]. Ionizable PEUs were prepared that could be cast into elastic membranes with good mechanical strength. Reversible swelling of the membranes was observed with increasing pH owing to the increasing hydrophilicity of the ionized carboxyl groups. At pH 8.5 the bulk membrane was completely disassembled as full dissolution of the polymer chains occurs. Cationic drugs and proteins were loaded into the networks with release being highly dependent on pH and ionic strength as expected. Conversely, incorporation of a tertiary amine containing diol can lead to cationic PEUs. Films prepared with dipeptide and *N*-methyldiethanolamine chain extenders exhibited a cationic surface in aqueous solution, which was shown to bind heparin (leading to a heparinized biofilm surface) with potential as an anticoagulation material [86]. It has been shown that bioactive molecules can be incorporated covalently into the polyurethane linkage as for example the amine containing antibacterial agent ciprofloxacin [87]. During polymer degradation the drug undergoes a slow and controlled release, potentially useful in antimicrobial applications. A polyurethane graft copolymer was prepared by employing a bis-isocyanate terminated poly(butyl acrylate) [88]. When reacted with PCL-diol, segmented copolymers were produced which aggregated into well defined nanofibers and were studied for use as adhesives. Varying amounts of non-polymeric bis-isocyanate could be added to alter the copolymer composition and ratio of each polymer block.

By inorporating diamino chain extenders instead of diols, poly(urethane urea)s (PUUR) can be produced with higher tensile strength and moduli compared to the less hydrogen-bonded polyurethanes. PUURs derived from PCL-diols, various diamino alkanes and diphenylmethane diisocyante, were prepared and spun into fibres with mechanical properties ideal for ligament reconstruction tissue engineering applications [89]. Incorporation of the elastase sensitive tripeptide motif Ala-Ala-Lys as a chain extending diamine leads to an interesting class of enzyme responsive PUURs with PCL as soft segment [90]. A high tensile strength material resulted and degradation studies showed that elastase, an enzyme intimate to extracellular matrix degradation, greatly increased the erosion rate. The surface could be functionalized with RGD containing peptides and the proliferation of varying endothelial cell lines was studied.

3.2.3 Segmented copolymers based on biopolymers

Natural biopolymers are good candidates for copolymerization, with polysaccharides being a versatile, biodegradable, and abundant pool for polymer science. Chitosans (CS) are a group of water soluble cationic copolymers of glucosamine and *N*-acetylglucosamine derived from partial deacetylation of chitin. Graft copolymers CS-*g*-PCl can be prepared by linkage of PCL to either free hydroxyl or free amino groups on the chitosan backbone. PCL-OH can be directly coupled to free amine groups by carbonyldiimidazole coupling but it is necessary to protect the free hydroxyl groups of the biopolymer [91]. Amphiphilic copolymers with up to 90 wt.% PCL were prepared and seen to aggregate into well defined nanoparticles with a cationic surface, with potential to bind polynucleotides for transfection. When free amino groups are protected with phthalic anhydride, it is possible to directly initiate ROP by standard tin catalyzed procedures initiated by primary alcohols on chitosan; microwave heating has been shown to aid this process [92, 93]. Subsequent liberation of the amino groups gives highly amphiphilic graft copolymers. An intriguing direct route to chitosan functionalized with PCL through only the alcohol groups uses cationic ring opening polymerization of CL with methanesulfonic acid as solvent and catalyst [94]. Graft copolymers of variable ratio were found to show favourable low toxicity and could be electospun when blended with PCL into very well defined nanofibres for potential tissue engineering applications. Phthaloyl protected CS was esterified with maleic ester functionalized mPEG-*b*-PCL to give the graft block copolymer CS-*g*-(mPEG-*b*-PCL) with variable compositions [95]. Upon amine deprotection, highly defined nanoaggregates were formed in aqueous solution, which could encapsulate hydrophobic species and are expected to

show interesting degradation profiles. Isocyanate functionalized PCL (prepared by selective reaction with an asymmetric bis-isocyanate) can also be linked to amine protected CS by carbamate linkage to give amphiphilic copolymers for drug encapsulation and release [94]. Heteroarm graft copolymers have been produced by sequentially linking mPEG-COOH and PCL (via ROP) to the CS hydroxyl groups with protected amino termini [96]. The resultant miktoarm graft copolymers aggregated to form stimuli sensitive nanoparticles with proposed switchable structural orientations depending on pH and solvent. In addition to chitosan, PCL has been attached to starch polymers or granules by either ring opening polymerization [97, 98], or through urethane linkage [99].

3.3 Supramolecular polymers

Although many properties of polymeric materials have some underlying supramolecular basis (e.g. the hard segments in the blockcopolymers described above), supramolecular polymer architectures are distinct as structures of physically crosslinked macromolecules bound together by moieties, which undergo specific and strong physical interactions by non-covalent bonds [100]. Due to the transitory nature of the crosslinks, a range of stimuli responsive behaviours can be achieved. Typically, crosslinks are made by complementary binding of polymer bound moieties through hydrogen bonding or other electrostatic effects. In essence, host/guest interactions between end-group functionalized oligomers act as non-covalent chain-extenders, leading to two- or three-dimensional architectures of higher order. In order to achieve a high level of integrity multiple interactions must operate cumulatively.

Various examples of defined architectures based around supramolecular interactions have been reported. Luminescent star block copolymers were prepared by coordination of bipyridyl-PCL (bpyPCL) and dibenzoylmethane-PLLA (dbmPLLA) macroligands to a Europium ion core to give a range of homo- and heteroarm complexes such as $Eu(dbmPLA)_3(bpyPCL_2)$ [101]. Thin films cast from heteroarm complexes showed highly defined microphase separation into lamellar structures; heating the films induced morphological changes due to the labile nature of the metal-ligand bonds. PCL grafted onto a dipyridinylpyradizine ligand was shown to complex Cu(I) ions in a highly stable [2 × 2] grid orientation with 4 macroligands per complex, leading essentially to a tetraarm star PCL with metal ion core [102]. This “supramolecular click” complexation was likened to the Sharpless/Huisgen copper catalyzed click conjugation of PCL-alkyne to an azide functionalized cyclodextrin core. PCLs attached to bipyridyl ligands have been shown to

complex Ruthenium salts to form complexes termed as “metallopolyesters” which were incorporated into polymeric films; applications in metallopharmaceuticals and imaging are conceivable [103, 104].

PCL chains are well known to complex cylclodextrins (CD) to form pseudorotaxanes. Studies have shown that CD inclusion in PCL films can modulate the enzymatic degradation rate as the CD lowers the hydrophobicity of the material [105]. Star ternary blockcopolymers based around a poly(ethyleneimine) (PEI) core with PCL-*b*-PEG arms were subjected to a detailed study in the ability to complex DNA and facilitate transfection [106]. Interestingly, sol-gel transitions were highly sensitive to the amount of α-CD added to the polymer in aqueous phase. The naked polymer caused a turbid suspension, which could fully dissolve at intermediate CD concentrations as the hydrophobic PCL arms were shielded (Figure 1). At higher CD concentrations gelation occurs, presumably due to supramolecular crosslinking. DNA polyplex formation was also highly sensitive to CD concentration. mPEG-*b*-PCL-*b*-mPEG copolymers were shown to undergo rapid supramolecular hydrogelation in the presence of α-CD; as neither component alone exhibits gelation, the system is ideal for use in injectable hydrogel applications [107]. Such biocompatible gels were able to slowly release encapsulated dextran as a test substrate and were able to encapsulate mesenchymal stem cells without affecting cell morphology. A study on site-isolated porphyrin core 4-arm PCL star polymers showed that the addition of α-CD could suppress crystallization of the PCL chains and also increase hydrophilicity and compatibility towards peptide drugs [108]. Porphyrin containing nanoarchitectures are of considerable interest for targeted photodynamic therapy and bioimaging.

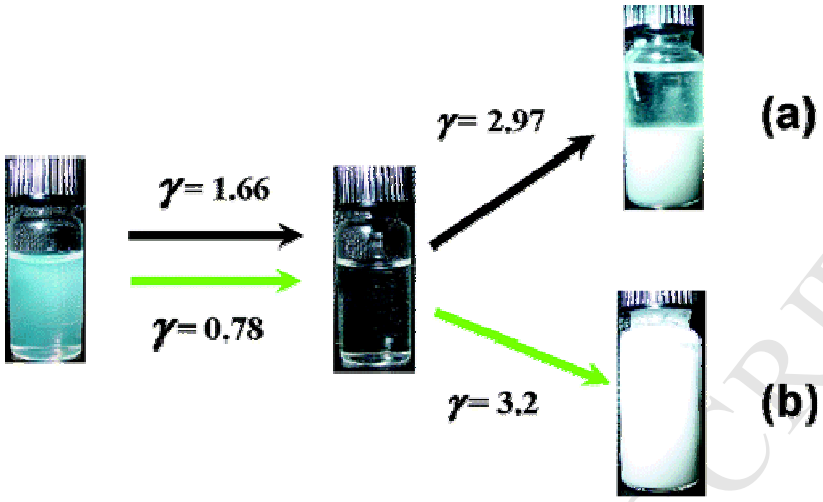


Figure 1 Phase transition phenomena of PEI25k-*g*-(PCL2k-*b*-PEG2k)$_{2.8}$ (a) and PEI25k-*g*-(PCL1.2k-*b*-PEG2k)$_{5.1}$ (b) upon adding α-CD solution. γ is the weight ratio of added α-CD and copolymer. Reprinted with permission from [106]. Copyright 2005 American Chemical Society.

Hydrogen bonding interactions can be utilized to control polymeric architectures with access to novel smart materials. PCL diol telechelics were functionalized to present self-complementary ureidopyrimidinone (UPy) quadruple hydrogen bond acceptor/donors either at the terminal ends or within the middle segment of the polymer chains [109]. Intimate mixing of such polymer chains in different ranges led to films with widely differing rheological properties. Similar materials with UPy functionalized PCL, poly(valerolactone) (PVL), and PCL-*ran*-PVL telechelics were investigated (Figure 2) [110]. Intimate mixing of PCL and PVL telechelics led to segmented supramolecular copolymers with rheological properties tunable by composition; in comparison, random supramolecular PCL-*ran*-PVL allowed less control over thermal and mechanical properties. Star-shaped UPy functionalized PCL with up to 4 arms were subjected to a detailed study on the rheological properties of supramolecular networks formed at different composition ratios [111]. Pronounced differences in thermal transition temperatures and mechanical properties were observed with the incorporation of reversible supramolecular linkages leading to a very complex system [111]. A series of polyureas based upon PCL as a component in a poly(urea urethane) were prepared and found to organise into nanoscale fibres by supramolecular interactions [109]. The resulting polymers could be processed into highly elastic films with good biocompatibility and mechanical properties comparable to soft tissues. Oligourea conjugated dyes could be incorporated into the films with slow release dependent on the degree of matching between polyurea motifs in

the polymer chains and in the dye. Incorporation of urea-labelled cell adhesion promoting peptide RGD into the films was possible. It is postulated that slow gradient release of RGD peptide from such films could initially promote cell adhesion and stimulate deposition of an extracellular matrix leading to a compatible biofilm. Fibroblasts could proliferate and adhere to the film surface comparable to cell-culture polystyrene. Hydrogen bonding between poly(acrylic acid) chains and the ester linkages in PEG-*b*-PCL have also been used to form biodegradable supramolecular gels with possibilities to encapsulate hydrophobic therapeutics [112].

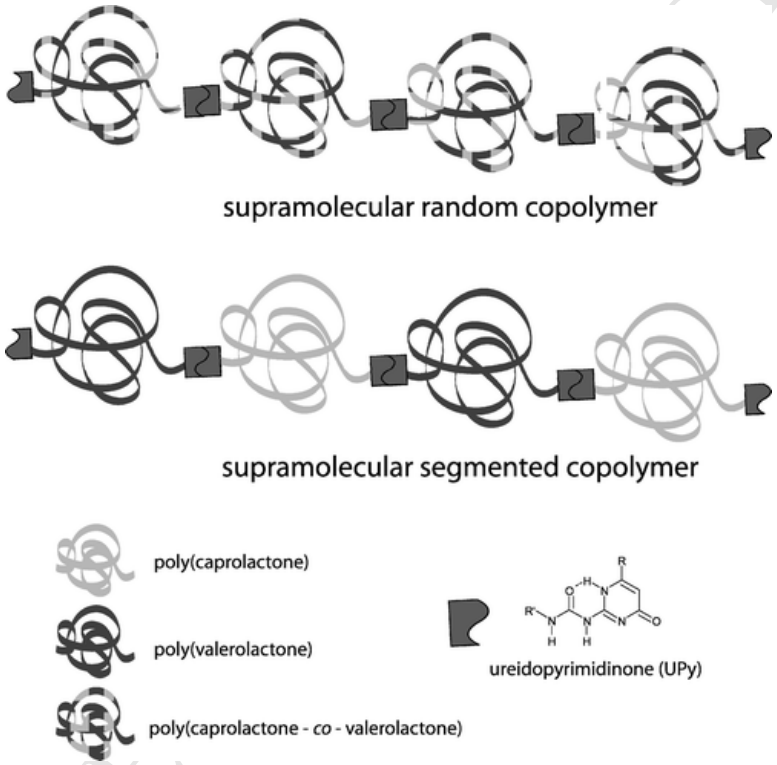


Figure 2 Schematic drawing of supramolecular polymers formed through hydrogen bonding of ureidopyrimidinone functionalized PCL telechelics and copolymers with poly(valerolactone). Reprinted with permission from [110]. Copyright 2007 American Chemical Society.

3.4 Star shaped and miktoarm polymers

3.4.1 Star shaped polymers

Ring opening polymerization by polyvalent initiators opens up numerous possibilities for PCL star polymers which have received much interest for various applications such as studying thermal behaviours, unimolecular micelles, and as components for polymer networks

[113]. Simple polyvalent initiators include trimethylolpropane, pentaerythritol and dipentaerythritol leading to 3, 4 and 6 armed stars respectively (Scheme 6) [114]. It has been shown that the melting temperature, crystallization temperature and degree of crystallinity reduces as the number of arms increases in comparisons between linear, tetrameric, and hexameric stars [115, 116]; star PCLs of more arms also crystallise slower than less branched analogues [117]. Lowered melting temperatures were also observed for trivalent glycerol-based PCL stars, which could be end functionalized with maleic anhydride as potential substrates for further reaction [118]. Thermal studies on porphyrin (8 arms) [119], phosphazene (6 arms) [120, 121], resorcinarene (4 arms) [122], cyclodextrin (7 arms) [123], star polystyrene (8 arms) [121], and silsesquioxane [124] (average 30 arms) star PCLs showed the same trend of lowering melting temperatures and in many cases significantly enhanced thermal stability compared to linear polymers of corresponding molecular weight. A silsesquioxane core was used to form 8 armed PCL stars where the arms were able to form inclusion complexes with α-cyclodextrin to afford novel architectures, although star PCLs complexed less cyclodextrin units relative to linear PCL due to steric hindrance near the core [125]. Some physical crosslinking of stars was postulated (one cyclodextrin can complex 2 distinct PCL chains). Porphyrin and pyrene cores have been modified with PCL arms to effectively isolate the chromophore and modify fluorescence quenching and FRET processes [126, 127]. Additionally, ε-caprolactone can be copolymerized with AB_2 monomers such as bis(hydroxymethyl)butyric acid to give hyperbranched copolyesters [128].

A series of 5-arm star poly(ethylene glycols) were used as macroinitiators to prepare a range of star-shaped block copolymers in parallel [129]. The resulting inverse unimolecular micelles were screened for encapsulation of various guests in two phase aqueous/organic systems. The behaviour of these amphiphilic copolymers at the water/air interface were studied in detail and were shown to be surface active [130]. As another polyether core, hyperbranched polyglycerol was used as a macroinitiator to form stars with up to 52 arms of variable length [131]. Such star PG-*co*-PCL blocks have been used to prepare size controlled silver nanoparticles by reduction of encapsulated silver salts [132]. A detailed study into the preparation of PG-*co*-PCL stars starting from linear and branched polyglycerol initiators was conducted using chemical ($Zn(Oct)_2$) or enzymatic (Lipase B) means to promote ring opening polymerization of ε-caprolactone [133]. The enzymatic method left a greater proportion of sterically hindered polyglycerol hydroxyl groups unreacted, leading to substantially different microstructures of product.

Various other block copolymer stars have been constructed by growing PCL chains from dendritic cores. Hyperbranched poly(ethyleneimine) cores were used as macroinitiator to produce PEI-*b*-PCL stars with up to 270 arms [134]. Polar dyes could be encapsulated within the formed unimolecular micelles and additionally the individual stars were found to self assemble to some extent and encapsulate material as an aggregate; the free hydoxyl groups on each PCL terminus could also be modifed by esterification to modify this behaviour. In a similar fashion, amphiphilic star polymers with hyperbranched poly(ester amide) cores showed excellent uptake of polar dyes into non-polar media with arm length and core sizes having a large influence on observed uptake [135]. Stars based around a dendritic poly(ether amide) core were prepared with the PCL chains having greater thermal stability and lower melting temperatures and crystallinity than linear analogues [136]. The free hydoxyl termini were esterified with PEG chains to make PEA-*b*-PCL-*b*-PEG stars with an inverse liposome architecture; such stars aggregated in water to form defined nanoparticles at low critical concentrations. Structurally related PEA-*b*-PCL-*b*-PNIPAM stars were then studied by esterifying poly(*N*-isopropylacrylamide) (PNIPAM) to the free PCL hydoxyl termini [137]. Once again aggregate nanoparticles were formed at low concentration and hydrophobic drugs could be solubilized in aqueous systems. Interestingly raising the temperature above LCST for PNIPAM renders the block hydrophobic leading to aggregate disruption; drug release from such systems was more rapid at 40 °C than 20 °C (LCST was observed around 32 °C). Dendritic polyamidoamine was used as a core to prepare structurally similar PAMAM-*b*-PCL-*b*-PEG stars which also showed good uptake of hydrophobic drugs in aqueous solutions below a critical aggregation concentration [138].

3.4.2 Miktoarm polymers

Very interesting complex star architectures as miktoarm or “mixed arm” polymers are possible via utilization of orthogonal polymerization reactions, such as ring opening polymerization, ATRP, NMP, RAFT and click conjugation, starting from a heteromultifunctional core [113]. As with conventional star PCLs, A_2B_2 PCL-*b*-PS miktoarm polymers radiating from a pentaerythritol core showed lower thermal transition temperatures and less crystallinity than linear analogues [139]. A basic building block for A_2B stars is the bromubutyrate monoester of trimethylolpropane which present two free hydroxyl groups for ROP of CL and one initiator for ATRP; miktoarm A_2B polymers of PCL copolymerized with methacrylates or styrenes were produced in an early example [140]. Typical access to ABC

miktoarms can be gained by starting with a low molecular weight initiator bearing a free hydroxyl group, an ATRP initiator branch (e.g. bromobutyrate), and an NMP initiator branch (e.g. TEMPO alkoxamine). Well controlled PCL-*b*-PS-*b*-PtBA miktoarms can be produced in this fashion by sequentially growing each chain, with PCL initiated by the free hydroxyl group in ROP [141]. Other methods of access to ABC miktoarms utilize click chemistry via PCL propargyl ether [142], or by initiating ROP of caprolactone at the junction of preformed AB block copolymers [143]. ABCD miktoarms of PCL-*b*-PtBA-*b*-PS-*b*-PMMA have been prepared by sequential NMP and free-radical polymerization addition of PS and PMMA at the junction of the PCL-*b*-PtBA macroinitiator preformed by diels-alder coupling [144]. A further example of an ABCD miktoarm by sequential polymerizations utilized ROP for CL, RAFT for MA and click conjugation of a PEG chain to give the PCL-*b*-PS-*b*-PMA-*b*-PEG miktoarm architecture [145]. Elegant access to A_3B_3 PCL-*b*-PMMA miktoarm star was reported by sequential polymerization on a six armed dendrimer with alternating free hydroxyl and bromobutyrate endgroups by ROP and ATRP respectively [140]. Cholic acid, a carboxylic acid containing triol steroid, was employed as a heterofunctional initiator to prepare A_3B PCL-*b*-PNIPAM with a combination of ROP and amide coupling of PNIPAM amine to the carboxyl end [146]. The resultant non-cytotoxic amphiphiles assembled into micelles in aqueous systems which could encapsulate hydrophobic drugs and exhibited thermosensitive drug release above the LCST of the PNIPAM chains (at approximately 37 °C).

Larger systems with multiple arms are possible from polyfunctional initiators. A block copolymer PCL-*b*-PS "macrodendron" with AB_8 architecture was prepared by sequential ROP followed by NMP on an aromatic oligoether initiator [147]. β-cyclodextrin can be used as a core; chemical differentiation of the 7 primary and 14 secondary hydoxyl groups can be achieved to give $A_{14}B_7$ miktoarm PCL-*b*-PEG facially amphiphilic polymers [148]. These structures self assembled to produce well defined nanoparticle aggregates which could be loaded with hydrophobic drugs. A PAMAM microgel with free amino and hydroxyl groups on the surface was sequentially decorated with discrete PEG and PCL chains through the amines and alcohols respectively [149]. With relevence to drug loading, interesting changes in the particle structure were observed in varied solvents such as in water (PCL chains collapse), in chloroform (PAMAM core collapsed) and in dimethysulfoxide (particle fully swollen) (Figure 3). Microgel cores with discrete PCL and PS arms have also been prepared in an elegant fashion [150]. PCL with a bromobutyrate endgroup was crosslinked with divinyl benzene by ATRP leading to a core shell microparticle with free bromide "living chain" endgroups for further PS grafting to core. The resulting particles were used to template the

formation of inorganic nanoparticles. Microgels surface functionalized with discrete PCL arms and either PS or PMMA heteroarms were produced in a similar fashion with a range of different cores including hyperbranched polyvinyl and hyperbranched polyester cores [151]. A wide variety of architectures were produced with interesting degradation profiles depending on the composition.

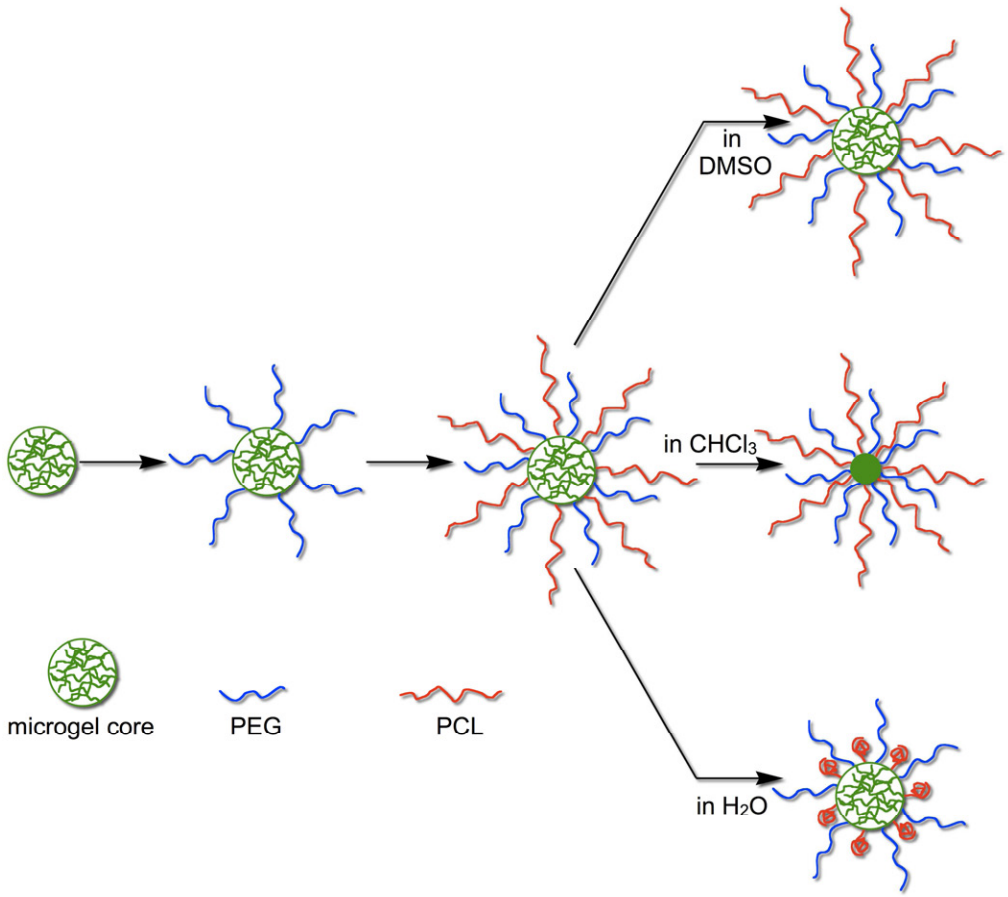


Figure 3 Solvent dependent switching of micellar structure of a PAMAM microgel with discrete PEG and PCL chains, modified from reference [149]. Copyright © 2008 Wiley Periodicals, Inc.

3.5 Polymer networks

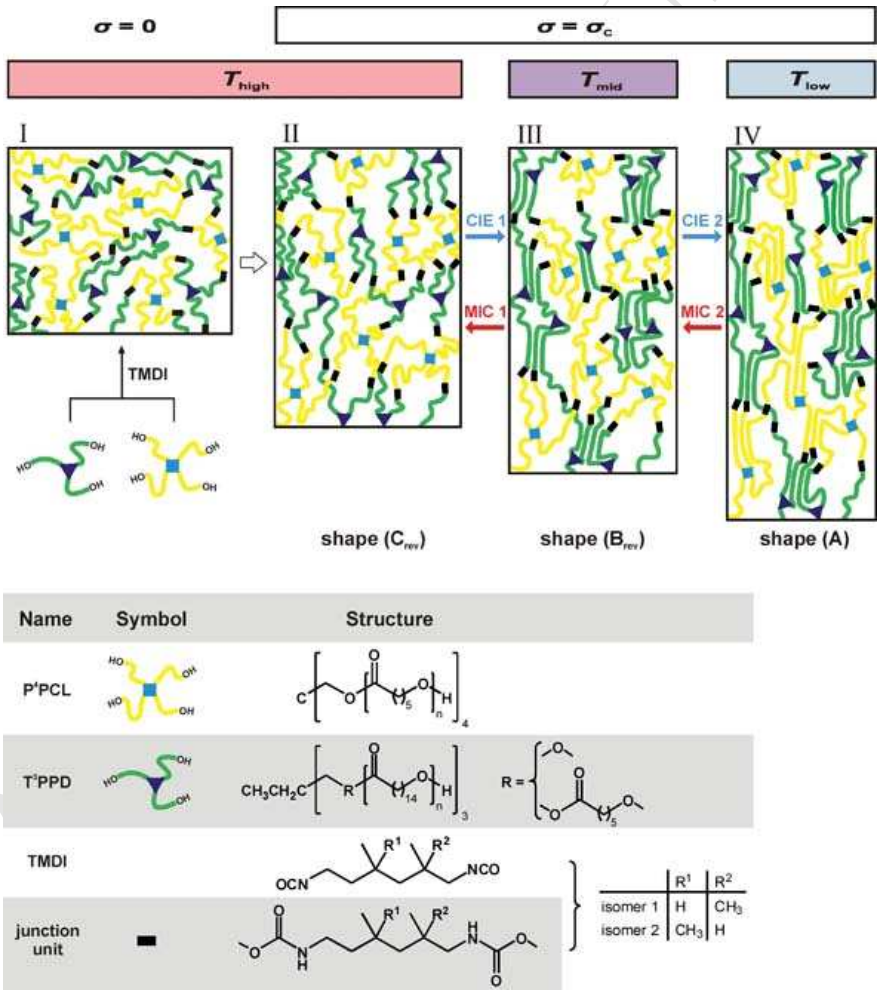
ε-caprolactone derived oligomers and polymers are interesting precursors for the preparation of covalent polymer networks due to their crystallization behaviour. Such networks have physical behaviours dependent on the density of the covalent network points. Below the melting temperature of the PCL-domains they exhibit physical crosslinks in addition to the covalent crosslinks, which can result in interesting thermoresponsive functions. An

established method to produce PCL-based networks relies on the covalent photochemical crosslinking of functionalized prepolymers. PCL diacrylate telechelics can be prepared through reaction of PCL with acryloyl chloride; photopolymerization then leads to networks having lowered melting points and crystallinity relative to the preformed macromonomers [152]. As chain sections near covalent network points have restricted mobility due to steric reasons, crystallization behaviour is influenced. Degradation rates of such materials are more rapid than linear PCL due to the lower crystallinity. Highly porous foams have been prepared by photpolymerization of PCL diacrylate in 'high internal phase emulsion' systems with the products showing good biocompatibility supporting fibroblast proliferation [153]. PCL-based PEUs have also been functionalized with photopolymerizable groups by incorporating hydroxyethyl methacrylate to the polymerization [154]. The resultant polyurethane acrylates were used as injectable gel forming systems with photopolymerization in situ.

Polymer networks derived from OCL dimethacrylates (obtained from the parent telechelic diol), are known to show shape-memory effects due to the interplay of the permanent polyacrylate covalent network and the thermoresponsive oligoester units. Switching temperatures are related to the melting temperature of the oligoester units, a property dependent on the average molecular weight of the macromonomers [155]. Additionally, macroscopic properties can be further influenced by incorporation of chain extender *n*-butyl acrylate, wherein a wide range of mechanical and thermal properties are achievable depending on crosslink density and composition [156]. Degradable networks composed of oligo[(*ε*-caprolactone-*co*-glycolide)] dimethacrylate and *n*-butyl acrylate with varying compositions are semicrystalline at room temperature with melting temperatures variable in the physiological range [157]. Increasing the amount of glycolate units in the parent dimethacrylate increases degradation rate, whereas an increase of the hydrophobic *n*-butyl acrylate component slows down degradation. Such systems have been studied for uptake and degradation promoted release of drugs in vitro and in vivo.[158] Crystallisable monomethyl PEG methacrylate has been copolymerised with OCL dimethacrylates to give covalent networks with varying chain crystallization behaviours at different temperatures, leading to multiple thermoresponsive phenomena.

An alternative method to produce covalently linked networks, utilizes diisocyanate-based condensation of star shaped PCL-based multi-ols to give (co)PEU networks, similar to multiblock copolymer synthesis mentioned previously. Such approaches are highly modular,

as the valency of the network point 'stars' can be modified, as well as the lengths of the polymer chain arms, and the chemical composition of copolymer systems. Star shaped PCL and PPDL segments, prepared from triol and tetraol initiators have been used to prepare co-PEU networks [159]. The application of two distinct crystallisable segments in a covalent network again leads to interesting thermoresponsive behaviours, variable by controlling the length of the polymer chain segments. Polymer networks subjected to constant strain underwent reversible melting-induced contraction (MIC) or crystallization-induced elongation (CIE) at temperatures relating to the melting temperatures of the distinct PCL and PPDL segments. (Scheme 8) Detailed investigations into the crystallization kinetics and behaviour of such segments in copolymer networks have been conducted in order to rationalise the observed shape-changing capabilities of the PCL/PPDL-based PEU architectures [160].



Scheme 8 Reversible shape change phenomena showing contraction or elongation of *co*-PEU networks prepared from star-shaped PCL and PPDL. Taken from [159]. Copyright © 2010 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

PCL diol can be chain extended by fumarate chloride to give a poly(caprolactone fumarate) macromonomer containing double bonds, which are susceptible to further crosslinking reactions [161]. Free radical initiated crosslinking in the presence of sodium chloride gave, after salt leaching, porous crosslinked materials with good biocompatibility. Poly(caprolactone fumarate) can also be crosslinked photochemically [162]. Three arm PCL, end group functionalized with maleic anhydride, was photochemically crosslinked with PEG diacrylate to give highly swellable polymer networks with hydrophobic and hydrophilic blocks for controlled release applications [163]. Star shaped PCLs based around a polyglycerol core were end functionalized with maleic anhydride or acrylate derivatives and crosslinked either photochemically or thermally with a peroxide initiator to give high gel content networks [164].

Various other copolymer networks have been prepared by assorted methods of physical or covalent crosslinking. PCLs were blended with poly(trimethylene carbonate) or the corresponding copolymers and crosslinked by gamma irradiation leading to soft elastic networks which were shown to be biocompatible and underwent controlled surface erosion [165]. Networks could be formed by chain extension of PCL diol with bisoxazolines with the resulting materials proving to be much more sensitive to enzymatic surface erosion compared to PCL diol alone. Semi interpenetrating networks prepared by the crosslinking of PEG diacrylate in the presence of PCL were studied for uptake and release of drugs with physical parameters such as degree of swelling and degradation rates being controlled by the ratio of macromonomers used [166]. Poly(ester anhydrides) prepared by copolymerization of sebacic acid and PCL derived anhydrides were studied as surface eroding films with the ability to slowly release bioactive agents for use in antifouling coatings [167]. Physical networks resulting from blends composed of PCL and biodegradable polymers such as chitosan [168], and poly(D,L-lactide) [169], have also been investigated for drug uptake and release applications. PCL stars with functional end groups can also be used as additives to other network forming systems such as epoxy networks to modify material properties [170].

4. Current applications of *ε*-caprolactone-based polymers

4.1 Particulate systems for drug release

PCL as a biocompatible and biodegradable polymer is suitable for long-term sustained

delivery of bioactive agents over a period of one year [171]. Products generated by hydrolysis are metabolized by the body either via tricarboxylic acid cycle or by renal secretion [172]. The major problem with some biodegradable polymers such as PLA and PLGA is the generation of acidic environments during degradation resulting in a pH of 2-3, which may lead to efficiency loss of the entrapped bioactive agent [173]. Slow degradation of PCL and the absence of acidic environment generation during its degradation make this polymer suitable for long term drug release. Furthermore, PCL's high solubility in organic solvents and its ability to blend with other macromolecules facilitate the creation of various potential structures as therapeutic agents [174]. The semicrystalline nature of PCL helps adjusting the release profile of the encapsulated agent. It has been reported that an increase in the crystallinity in the structure reduces the permeability by decreasing the solubility of the entrapped drug and increases the tortuosity of the diffusional pathway [175].

Colloidal PCL-based systems have attracted great interest over the last three decades in view of their application as drug delivery vehicles [176, 177]. Self-assembled (micellar) and particulate structures have been widely investigated as encapsulators of several drugs and proteins [178]. Utilization of nano carrier agents in drug delivery emerged from the need for new delivery vehicles for bioactive agents which would provide the pharmocokinetic profiles that mimic the normal pattern of those agents [179], where the effectiveness of many of those agents, in the context of their therapeutic index and selectivity, is restricted [179, 180]. Encapsulation methods enhance and prolong the stability of the bioactive agents [181], improving the therapeutic efficiency by adjusting the exact amount of the agent for the right therapeutic response, preventing degradation and nonspecific uptake by the cells, thus minimizing side effects [182]. The structure of a carrier system has a strong impact on the loading of bioactive agents, and affects their release, cellular internalization, and in vivo biodistribution [183, 184]. Micellar structures and micro- or nanoparticles of various morphologies allow for more control over degradation rates, drug release behaviour, or partitioning within the body (Figure 4) [185, 186].

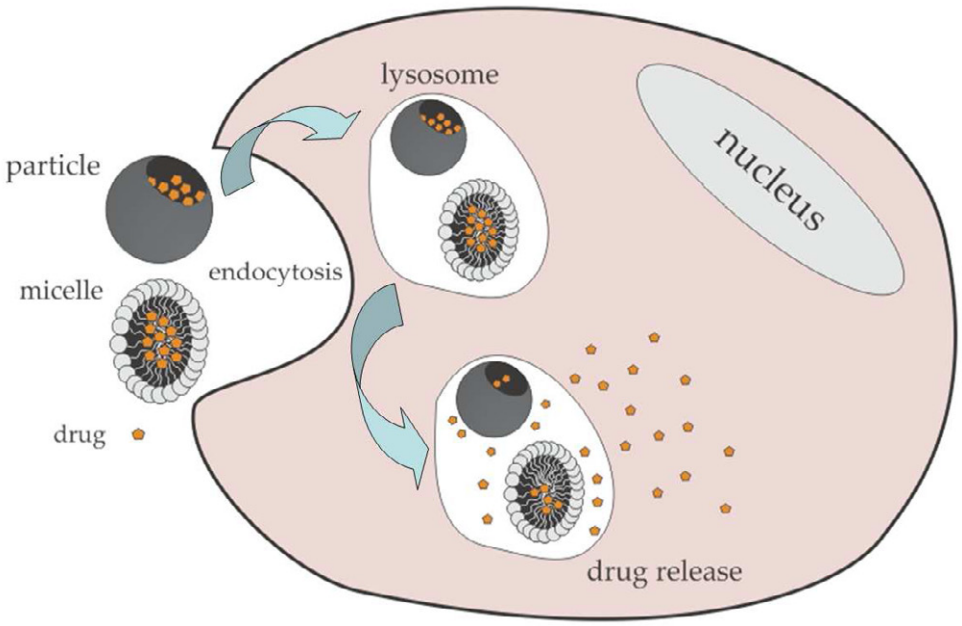


Figure 4 Schematic showing PCL nanoparticle uptake by cells and consequent drug release.

4.1.1 Micellar structures

The amphiphilic nature of block copolymers leads to a self-assembled structure of various morphologies such as spherical micelles, worm-like micelles and vesicles [187]. Among those morphologies, spherical micelles are the structures having a diameter less than 200 nm consisting of a hydrophobic inner core and hydrophobic outer shell in aqueous media, or the opposite in non-aqueous media [188]. Choice of creating a hydrophilic or hydrophobic core is based on the entrapped bioactive agent's hydrophilic or hydrophobic nature. PCL is one of the most commonly used polymers to create the hydrophobic block in micellar structures for drug delivery. The development of di- or triblock copolymer micelles as drug delivery agents has greatly enhanced since the beginning of the 1980s with many emerging variations in the type of polymers used based on a hydrophobic-hydrophilic block structure [189, 190]. Some examples investigated as hydrophilic segments are poly(ethylene glycol) (PEG) [191], cationic polymers such as poly(ethyleneimine) (PEI), poly(4-vinyl pyridine), polylysine, poly(*N*-methyldietheneamine sabacate), chitosan [192], or polyelectrolytes such as poly(aspartic acid) for stimuli sensitive structures [193].

Poly(ethylene glycol)-*block*-poly(*ε*-caprolactone) (PEG-*b*-PCL) copolymer micelles were reported as delivery vehicles for dihydrotestosterone for androgen replacement therapy where many of the oral androgen formulations have been found to have low efficiency because of

rapid clearance by the liver [179]. Related systems were found to be able to deliver hydrophobic neurotrophic agents, and stimulate neuronal outgrowth in selected cell lines in vitro [191]. PEG-*b*-PCL micelles containing gold nanoparticles were developed as a new approach for labeling biodegradable block copolymer micelles of potential biological applications, such as tissue and subcellular localization [194]. There is evidence that worm-like micelles of PEO-*b*-PCL appear to be more promising as nanocarriers with improved solubilization efficiency, and enhanced stability when compared to spherical micelles [187]. Cationic chitosan-*graft*-poly(*ε*-caprolactone) brush-like copolymers were synthesized for 7-ethyl-10-hydroxy-camptothecin (SN-38) encapsulation as a topoisomerase I inhibitor against several tumor cell lines [192]. A novel thermosensitive micellar structure composed of poly(ethylene glycol)-poly(*ε*-caprolactone)-poly(ethylene glycol) triblock copolymer, wherein chemotherapeutics are encapsulated, was proposed as an injectable-gel delivery system, showing a sol-gel transition around body temperature [195]. Amphiphilic block copolymeric micelles composed of mPEG-PCL have been prepared for indomethacin delivery [188]. The micelles formed were less than 200 nm in diameter and exhibited efficient penetration through the sinusoidal capillaries. Significantly, an increase of indomethacin, as a hydrophobic drug, enhanced interactions between the hydrophobic PCL blocks, resulting in a decrease of drug release. Hydrophobic PCL was grafted onto a hydrophilic poly(vinyl alcohol) backbone to give graft copolymers PCL-*g*-PVA which could assemble into nanostructures able to encapsulate both hydrophilic and hydrophobic drugs in different environments [196]. This is due to switching between different self assembled states in polar or non-polar environments.

4.1.2 Nano- and microparticulate structures

Micro- and nanoparticles are defined as solid spherical particles presenting small size and volume, large surface area, ability to diffuse and variety of size, surface chemistry, composition, morphology and topogrophy [172, 197]. The direct preparation of PCL in heterogeneous systems is an excellent method to prepare nano- and microscale materials with defined dimensions through dispersion polymerization [198]. Particulate structures, which are encapsulating various drugs (anaesthetics, antibiotics, antiparasites, antitumorals, enzymes, hormones, proteins etc.) [199], have several routes of administration such as intravenous, oral, pulmonary, nasal and ocular [200]. A commonly used method for encapsulation of drugs within polymers such as PCL and its copolymers is the multiple emulsion solvent evaporation method (Figure 5) [197]. The desired polymer and drug are dissolved in an organic solvent which is then emulsified in an aqueous or oil phase containing emulsifier. During evaporation

of the organic solvent, the microspheres are hardened and can be collected by filtration and drying [201]. The preparation and characterization of protein-loaded PCL microparticles for oral vaccine delivery was investigated, where bovine serum albumin (BSA) was used as model antigen for encapsulation. The study showed the BSA release from the particles, which ensures the entrapped protein remains unaltered by the encapsulation process [173]. PCL microparticles are reported in the literature and analyzed as an encapsulating agent for the bioactive agents such as cyclosporine A (CsA) as an immunosuppressive agent used primarily to reduce the incidence of graft rejection in recipients of transplanted organs [178, 202], atovaquone [203], and amphotericin B [204], as in vitro antileishmaniasis drugs, heparin as an antocoagulant used for the treatment and the prevention of deep vein thrombosis and pulmonary embolism [205], magnetic microparticles (MMP) as potential agents for utility in magnetic resonance imaging (MRI) [206], Levobunolol as an agent used in the topical treatment of increased intraocular pressure due to chronic open-angle glaucoma or ocular hypertension [207], and felodipine, as a drug used in the treatment of hypertension [197].

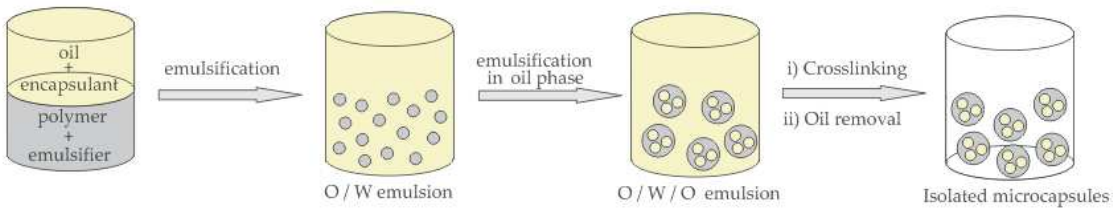


Figure 5 Scheme showing the preparation of PCL nano/microparticles by a double emulsion method.

Both PCL homo- and copolymers are used to prepare particulate structures as drug carriers, with the high miscibility of PCL and other polymers being advantageous. Nanoparticles were prepared composed of nonionic methoxy poly(ethylene glycol)/poly(ε-caprolactone) (mPEG/PCL) and amine-terminated mPEG/PCL amphiphilic diblock copolymers with variations of copolymer molecular weights and molar compositions of mPEG and PCL, showing that mPEG/PCL nanoparticles with cationic charge groups exhibited higher DNA transfection efficiencies when compared to the nonionic mPEG/PCL nanoparticles, which is proposed as a better potential carrier system for DNA delivery [208]. A novel nanoparticle structure composed of a polyester and a polysaccharide was shown by using amphiphilic copolymers based on dextran grafted with PCL side chains (PCL-DEX). Dextran was proposed as an alternative to PEG to form nanocarriers where non-specific protein adsorption is avoided [200].

Current technology necessitates the use of large amount of organic solvents for micro- and nanostructure preparation, which should be avoided concerning environmental issues [209]. Supercritical fluid (SCF) extraction method is proposed as an alternative to the traditional methods using organic solvents as the method makes it possible to separate a particular component from a multicomponent nature by the selective solvating method of the SCF, which is due to the modification of density hence the solubilizing power of the SCF with small changes in temperature and pressure near the critical point [210]. A novel nanostructured polymeric composite of PCL and ultra-high-molecular-weight polyethylene (UHMWPE) was producible by using supercritical carbon dioxide. With this method, PCL and UHMWPE could be blended overcoming the difficulties in processing UHMWPE and instability of PCL at elevated temperatures [211]. Another solvent free preparation of caprolactone oligomer microspheres where estradiol, a hydrophobic drug, is encapsulated was reported. Microspheres were obtained by coaggregation of melted PCL and mPEG–PCL in the absence of any organic solvent and a subsequent quenching process to 0 °C, and it was shown that the release kinetics of the entrapped drug was dependent on the loaded amount [212].

4.2 Surface functionalization of PCL-based polymers

As the majority of research on PCL networks and films historically has been focussed on biomaterial applications, there are many studies on material surface interactions with biological moieties and how surfaces can be tailored towards specific goals. A comparative study on fibroblast and osteoblast adherence to film blends with varying PLLA and PCL amounts was made along with films from varied block copolymers PLLA-*b*-PCl [213]. All samples were suitable for cell growth with few significant differences but certain block copolymers showed outstanding results; surface patterning from microphase separation can have a large effect on surface interactions with cells [214]. Wettability is another important factor governing surface interactions. Plasma treatment can be used to incorporate carboxylate and hydroxyl groups to PCL surfaces increasing the hydrophilicity and increasing roughness with aging [215]. Conversely, low surface energy hydrophobic films have been prepared as polyurethanes based upon perfluroalkane terminated PCLs and poly(*γ*-*t*-butyl-*ε*-caprolactone)s [216]. Treatment of PCL surfaces with alkaline solutions can hydrolyse surface esters and add carboxylate functionality, thus changing the surface chemistry markedly and increasing wettability. Absorption of common serum proteins such as albumin,

collagen and fibronectin occurs much more readily to alkaline treated PCL membranes resulting in a surface biofilm [217]. Biomarkers specific for heparin and/or insulin were attached to plasma treated PCl surfaces by amide linkage to give surfaces with enhanced biopolymer immobilization properties; this had pronounced effects on fibroblast adhesion, particularly with heparin [218]. Surface charge plays a critical role in interactions as was investigated by studying endothelial cell adhesion to switching positive and negative surfaces prepared by successive layer-by-layer assembly of poly(styrene sulfonate) polyanion or collagen [219]. The initial PCL surface was rendered cationic by partial aminolysis of surface esters by diaminoalkanes. No proliferation occurred on the anionic surface but the collagen surface was favourable to the cells adhesion. Micropatterning techniques can be applied to PCL surfaces, biomolecules such as chitosan and albumin were micro transferred onto a preactivated aldehyde containing surface in a well controlled and precise procedure [220].

Multiple techniques to synthetically adjust surfaces with complex chemical modifications have been reported. In a well studied procedure, aminolysis of estergroups by a diaminoalkane can be used to append an amino functionalized chain, to which RGD containing peptide sequences were conjugated. Fibroblast adhesion tests were conducted on pure PCL, PCL amine and PCL-RGD functionalized surfaces with very clear preference of cells to form focal adhesion complexes on the peptide functionalized surface (Figure 6) [221]. An alternative method to include surface functional groups utilizes copolymers of PCL and poly(γ-keto-ε-caprolactone) to introduce ketone functionality to the polymer chain which can be transformed to a linker for further modification through hydrazone linkage [222]. Through this process surfaces could be modified with RGD peptide sequences or polylysines which again had a pronounced effect on cell adhesion and surface chemistry respectively. Poly(acrylic acid) can be grafted directly from the PCL surface by an electron beam initiation method [223]. The resulting carboxylate groups were conjugated to a linker and RGD peptides attached. Poly(methacrylic acid) chains have been grafted from PCL by photo-oxidizing the surface with peroxides which fragment into radical initiators for graft polymerization in a controllable fashion [224]. Such functionalization has profound effects on surface wettability and chemistry. Biomolecules such as gelatin could be covalently attached by amide chemistry and functionalized films showed improved cytocompatibility. Photoinitiated polymerization of acrylamide has been reported to prepare surface bound graft copolymers [225]. Subsequent reduction of the polyacrylamide chains to polyamines could be achieved, to which heparin was conjugated by reductive amination for a 3-step

biofunctionalization procedure. Bone morphogenetic proteins could be immobilized within the heparin coating and the whole system was used to cultivate mesenchymal stem cells with enhanced proliferation over non-modified surfaces. Access to a surface initiator for ATRP can be gained by partial hydrolysis of surface PCL esters and esterification to a bromobutyrate [226]. Poly(glycidyl methacrylate) chains were polymerized and further reacted through the epoxy groups with cell adhesion promoting groups such RGD peptides or collagen.

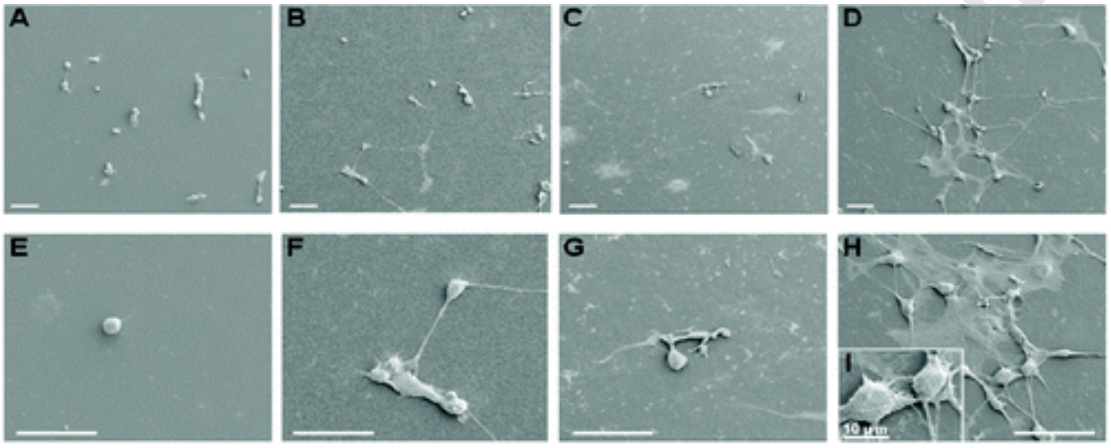


Figure 6. Scanning electron microscope micrographs (A and E PCL; B and F PCL-NH_2; C and G PCL-linker-GYDGR; D, H, and I PCL-linker-GRGDY). Bar 50 μm. Reprinted with permission from [221]. Copyright 2010 American Chemical Society.

4.3 Shape-memory polymers

The “shape-memory effect” observed in polymer networks is an interesting and potentially very useful phenomenon, in which a material can be deformed from a permanent shape and fixed in a temporary shape, which upon a given stimulus rapidly reverts to the permanent shape [227, 228]. The basis of this effect in thermoplastic shape-memory polymers is the microphase separation of networks into hard and switching domains. The hard segments “remember” the network integrity of the permanent shape by physical or covalent crosslinks. The switching domains are elastic above a certain switching temperature, above which external forces are applied to produce a temporary shape. Upon cooling the switching domains solidify and thereby fix the temporary shape. The crystallization behaviour and biodegradability of PCLs have made them particularly useful as switching segments in shape-memory polymers with switching temperatures in a useful range and excellent (generally up to 100%) shape recovery [78, 79]. PCL-based polyurethanes are one class of materials that can show shape-memory behaviour with the hard segments arising from the polyurethane

segments forming physical networks [229]. Multiblock copolymers that phase segregate into hard and switching domains are well known for shape-memory effects, particularly the PEUs described in section 3.2.2 and exemplified in scheme 7.

Covalent polymer networks of the type described in section 3.5 are also capable of exhibiting shape-memory behaviour. AB copolymer networks prepared by photocuring of PCL dimethacrylate and *n*-butylacrylate showed excellent shape-memory effect [156]. Changes in macroscopic properties such as reduced melting temperature and modulus of the system were observed as the amount of comonomer increased leading to a highly tunable system. Homopolymer networks of crosslinked PCL dimethacrylate also show shape-memory effect with switching temperatures and other mechanical properties being dependent on the molecular weight of the PCL prepolymers [155]. Triple shape-memory materials with two distinct switching temperatures and temporary shapes have been prepared by urethane crosslinking star shaped PCL and poly(*ω*-pentadecalactone) segments with different melting temperatures as shown in Scheme 8 [159].

Networks prepared by cross-linking multiarm polyglycerol-based PCL stars with diisocyanates exhibited a shape-memory effect with sharp thermal transitions around body temperature. Such networks were loaded with model drugs at the crosslinking stage and slow controlled release was observed from the networks above the switching temperature (37 ^{o}C) [230]. Likewise, shape-memory materials based upon urethane linked star shaped PCLs with a silsesquioxane core have been reported [231]. An interesting approach to shape-memory networks makes use of photoreactive cinnamic acid containing diacid chloride chain extender for block copolymers of diol telechelic PCL and PLLA [232], or PEG [233]. The cinnamic acid groups are crosslinked by photoinitiated [2 + 2] cycloaddition to form network points with switching temperatures tuned to around 38 °C to 45 °C by controlling the prepolymer ratios [234]. An alternative route to shape-memory materials goes via direct crosslinking of blended polymers. Carboxylic acid terminated telechelic PCL could be cross-linked with epoxidized natural rubber at elevated temperature [235]. PCL blended with a polymethylvinylsiloxane has also been radiation crosslinked to provide shape-memory networks [236]. It has been observed that films derived from PCL with partial inclusion complexes of *α*-CD do exhibit a supramolecular shape-memory effect as microdomains form

between crystallizable naked PCL chains and the fixed crystalline domains of the inclusion complex which serve to hold the permanent shape [237].

5. Outlook

In the re-emergence of PCL as a polymer of modern interest, much use has been found for ε-caprolactone-based segments in advanced copolymer architectures. Here, telechelic OCLs are a particularly versatile building block, along with ε-caprolactone-based copolymer diols. Many methods have been developed to substitute telechelic endgroups or to utilize PCL as a macroinitiator for block copolymer synthesis, such as by living polymerization methods. These synthetic methods are also being applied to biopolymer substrates to further expand the range of copolymers under study. It is evident that there is much scope for designing copolymer systems and architectures with highly defined material properties.

Self assembled particulate structures such as block copolymer micelles have been intensively investigated for drug delivery applications, and PCL chains being relatively mobile make ideal hydrophobic blocks. ‘Unimolecular micelles’ can be prepared containing PCL segments as star shaped block copolymers. The versatility of PCL chemistry is being employed in the preparation of intricate miktoarm star polymers, where the hydrophobic nature of the PCL chain leads to new amphiphile variants with novel behaviours. There have also been exciting developments in the field of supramolecular polymers containing PCL segments, with applications such as thermoresponsive hydrogels being pursued.

There has been significant progress in medical devices which are based on shape-memory polymers with switching temperatures around body temperature. Uses include self closing sutures and smart catheters. In this respect, recent advances in PCL-based copolymer networks have shown excellent potential, either through star shaped PCL-based PEUs, or through PCL dimethacrylate-based systems, amongst others. Actively moving implant materials that degrade to release a drug payload are an example of complex multifunctional materials. Advances have also been made in the fields of tissue engineering and implant materials, benefiting from the tunable properties of the more recent PCL-based materials. With the renewed interest in PCL it can be expected that commercial applications will be forthcoming in the biomedical field. The last couple of decades have seen exciting

developments in synthetic polymer chemistry and it is clear that PCL has a key role in the future.

6. References

1. Jenkins MJ and Harrison KL. Polym Advan Technol 2006;17:474-478.
2. Kulkarni A, Reiche J, Kratz K, Kamusewitz H, Sokolov IM, and Lendlein A. Langmuir 2007;23:12202-12207.
3. Karimi M, Heuchel M, Weigel T, Schossig M, Hofmann D, and Lendlein A. J Supercrit Fluid 2012;61:175-190.
4. Nair LS and Laurencin CT. Progr Polym Sci 2007;32:762-798.
5. Ulery BD, Nair LS, and Laurencin CT. J Polym Sci Part B Polym Phys 2011;49:832-864.
6. Woodruff MA and Hutmacher DW. Progr Polym Sci 2010;35:1217-1256.
7. Zhuravlev E, Schmelzer JWP, Wunderlich B, and Schick C. Polymer 2011;52:1983-1997.
8. Penczek S, Cypryk M, Duda A, Kubisa P and Slomkowski S. Progr Polym Sci 2007; 32:247-282
9. Duda A. ROP of Cyclic Esters. Mechanisms of Ionic and Coordination Processes. In: Matyjaszewski K and Moeller M, editors. Polymer Science: A Comprehensive Reference, vol. 4. Amsterdam: Elsevier, 2012. pp. 213-246.
10. Labet M and Thielemans W. Chem Soc Rev 2009;38:3484-3504.
11. Okada M. Progr Polym Sci 2002;27:87-133.
12. Dash TK and Konkimalla VB. J Contr Rel 2012;158:15-33.
13. Cai Q, Bei JZ, and Wang SG. J Biomater Sci Polym Ed 2000;11:273-288.
14. Hu YQ and Zhu KJ. Polym Degrad Stabil 2004;85:705-712.
15. Wang SG, Cai Q, and Bei JZ. Macromol Symp 2003;195:263-268.
16. Kasperczyk J, Hu YF, Jaworskam J, Dobrzynski P, Wei J, and Li SM. J Appl Polym Sci 2008;107:3258-3266.
17. Weiss RM, Jones EM, Shafer DE, Stayshich RM, and Meyer TY. J Polym Sci Part A Polym Chem 2011;49:1847-1855.
18. Dubois P, Degee P, Jerome R, and Teyssie P. Macromolecules 1993;26:2730-2735.
19. Baez JE, Marcos-Fernandez A, Lebron-Aguilar R, and Martinez-Richa A. Polymer 2006;47:8420-8429.
20. Kloss J, Munaro M, De Souza GP, Gulmine JV, Wang SH, Zawadzki S, and Akcelrud L. J Polym Sci Part A Polym Chem 2002;40:4117-4130.
21. Lendlein A, Neuenschwander P, and Suter UW. Macromol Chem Phys 2000;201:1067-1076.
22. Guillaume SM, Schappacher M, and Soum A. Macromolecules 2003;36:54-60.
23. Hwang MJ, Suh JM, Bae YH, Kim SW, and Jeong B. Biomacromolecules 2005;6:885-890.
24. Ferruti P, Mancin I, Ranucci E, De Felice C, Latini G, and Laus M. Biomacromolecules 2003;4:181-188.
25. Wang M, Zhang Q, and Wooley KL. Biomacromolecules 2001;2:1206-1213.
26. Wang SF, Lu LC, Gruetzmacher JA, Currier BL, and Yaszemski MJ. Biomater 2006;27:832-841.
27. Ponsart S, Coudane J, and Vert M. Biomacromolecules 2000;1:275-281.
28. Kricheldorf HR and Hauser K. Biomacromolecules 2001;2:1110-1115.
29. Schappacher M, Soum A, and Guillaume SM. Biomacromolecules 2006;7(4):1373-1379.

30. Toncheva NV and Mateva RP. Adv Polym Technol 2007;26:121-131.
31. Ferreira P, Coelho JFJ, and Gil MH. Int J Pharm 2008;352:172-181.
32. Clement B, Trimaille T, Alluin O, Gigmes D, Mabrouk K, Feron F, Decherchi P, Marqueste T, and Bertin D. Biomacromolecules 2009;10:1436-1445.
33. Lu FZ, Xiong XY, Li ZC, Du FS, Zhang BY, and Li FM. Bioconj Chem 2002;13:1159-1162.
34. Le Hellaye M, Fortin N, Guilloteau J, Soum A, Lecommandoux S, and Guillaume SM. Biomacromolecules 2008;9:1924-1933.
35. Zhou JX, Wang WX, Villarroya S, Thurecht KJ, and Howdle SM. Chem Commun 2008;44:5806-5808.
36. Stoilova O, Jerome C, Detrembleur C, Mouithys-Mickalad A, Manolova N, Rashkov I, and Jerome R. Chem Mater 2006;18:4917-4923.
37. Stoilova O, Jerome C, Detrembleur C, Mouithys-Mickalad A, Manolova N, Rashkov I, and Jerome R. Polymer 2007;48:1835-1843.
38. Sinnwell S, Inglis AJ, Stenzel MH, and Barner-Kowollik C. Macromol Rapid Comm 2008;29:1090-1096.
39. Gou PF, Zhu WP, Zhu N, and Shen ZQ. J Polym Sci Part A Polym Chem 2009;47:2905-2916.
40. Li HY, Riva R, Kricheldorf HR, Jerome R, and Lecomte P. Chem Eur J 2008;14:358-368.
41. Xiong XQ and Xu YH. Polym Bull 2010;65:455-463.
42. Carrot G, Hilborn JG, Trollsas M, and Hedrick JL. Macromolecules 1999;32:5264-5269.
43. Hedfors C, Ostmark E, Malmstrom E, Hult K, and Martinelle M. Macromolecules 2005;38:647-649.
44. Wiltshire JT and Qiao GG. J Polym Sci Part A Polym Chem 2009;47:1485-1498.
45. Wu DQ, Li ZY, Li C, Fan JJ, Lu B, Chang C, Cheng SX, Zhang XZ, and Zhuo RX. Pharm Res 2010;27:187-199.
46. Zhang B, Li YP, Sun JH, Wang SW, Zhao YL, and Wu ZY. Polym Int 2009;58:752-761.
47. Motala-Timol S and Jhurry D. Polym Int 2007;56:1053-1062.
48. Hedrick JL, Trollsas M, Hawker CJ, Atthoff B, Claesson H, Heise A, Miller RD, Mecerreyes D, Jerome R, and Dubois P. Macromolecules 1998;31:8691-8705.
49. Jia ZF, Zhou YF, and Yan DY. J Polym Sci Part A Polym Chem 2005;43:6534-6544.
50. Schramm OG, Pavlov GM, van Erp HP, Meier MAR, Hoogenboom R, and Schubert US. Macromolecules 2009;42:1808-1816.
51. Chen J, Zhang HL, Chen JF, Wang XZ, and Wang XY. J Macromol Sci Pure Appl Chem 2005;A42:1247-1257.
52. Shi M, Zhang HL, Chen J, Wan XY, and Zhou QF. Polym Bull 2004;52:401-408.
53. Lele BS and Leroux JC. Polymer 2002;43:5595-5606.
54. Perret R and Skoulios A. Makromol Chem 1972;162:143-162.
55. Liu CB, Gong CY, Huang MJ, Wang JW, Pan YF, De Zhang Y, Li GZ, Gou ML, Wang K, Tu MJ, Wei YQ, and Qian ZY. J Biomed Mater Res Part B Appl Biomater 2008;84B:165-175.
56. Bae SJ, Suh JM, Sohn YS, Bae YH, Kim SW, and Jeong B. Macromolecules 2005;38:5260-5265.
57. An JH, Kim HS, Chung DJ, Lee DS, and Kim S. J Mater Sci 2001;36:715-722.
58. Ryu JG, Jeong YI, Kim IS, Lee JH, Nah JW, and Kim SH. Int J Pharm 2000;200:231-242.
59. Quaglia F, Ostacolo L, Nese G, Canciello M, De Rosa G, Ungaro F, Palumbo R, La Rotonda MI, and Maglio G. J Biomed Mater Res Part A 2008;87A:563-574.

60. Kricheldorf HR, Fechner B, Shikanov A, and Domb A. Biomacromolecules 2003;4:950-955.
61. Huang MH, Li SM, Hutmacher DW, Schantz JT, Vacanti CA, Braud C, and Vert M. J Biomed Mater Res Part A 2004;69A:417-427.
62. Li SM, Garreau H, Pauvert B, McGrath J, Toniolo A, and Vert M. Biomacromolecules 2002;3:525-530.
63. Zastre J, Jackson J, and Burt H. Pharm Res 2004;21:1489-1497.
64. Zastre J, Jackson JK, Wong W, and Burt HM. J Pharm Sci 2007;96:864-875.
65. Elamanchili P, McEachern C, and Burt H. J Pharm Sci 2009;98:945-958.
66. Kang YM, Lee SH, Lee JY, Son JS, Kim BS, Lee B, Chun HJ, Min BH, Kim JH, and Kim MS. Biomaterials 2010;31:2453-2460.
67. Rieger J, Dubois P, Jerome R, and Jerome C. Langmuir 2006;22:7471-7479.
68. Rieger J, Passirani C, Benoit JP, Van Butsele K, Jerome R, and Jerome C. Adv Funct Mater 2006;16:1506-1514.
69. Petrova S, Riva R, Jerome C, Lecomte P, and Mateva R. Eur Polym J 2009;45:3442-3450.
70. Shuai XT, Porbeni FE, Wei M, Shin ID, and Tonelli AE. Macromolecules 2001;34:7355-7361.
71. Shuai XT, Wei M, Porbeni FE, Bullions TA, and Tonelli AE. Biomacromolecules 2002;3:201-207.
72. Bogdanov B, Toncheva V, and Schacht E. J Therm Anal Calorim 1999;56:1115-1121.
73. Gorna K, Polowinski S, and Gogolewski S. J Polym Sci Part A Polym Chem 2002;40:156-170.
74. Skarja GA and Woodhouse KA. J Biomater Sci Polym Ed 2001;12:851-873.
75. deGroot JH, deVrijer R, Pennings AJ, Klompmaker J, Veth RPH, and Jansen HWB. Biomater 1996;17:163-173.
76. Lendlein A, Neuenschwander P, and Suter UW. Macromol Chem Phys 1998;199:2785-2796.
77. Ciardelli G, Saad B, Lendlein A, Neuenschwander P, and Suter UW. Macromol Chem Phys 1997;198:1481-1498.
78. Lendlein A and Langer R. Science 2002;296:1673-1676.
79. Kratz K, Voigt U, and Lendlein A. Adv Funct Mater 2012;22:3057-3065.
80. Gorna K and Gogolewski S. J Biomed Mater Res 2002;60:592-606.
81. Skarja GA and Woodhouse KA. Journal of Biomater Sci Polym Ed 1998;9:271-295.
82. Zhang CH, Zhang N, and Wen XJ. J Biomed Mater Res Part B Appl Biomater 2006;79B:335-344.
83. Cao XD, Chang PR, and Huneault MA. Carbohyd Polym 2008;71:119-125.
84. Santayanon R and Wootthikanokkhan J. Carbohyd Polym 2003;51:17-24.
85. Zhang CH, Zhao KJ, Hu TY, Cui XF, Brown N, and Boland T. J Contr Rel 2008;131:128-136.
86. Buruiana EC and Buruiana T. J Biomater Sci Polym Ed 2004;15:781-795.
87. Woo GLY, Mittelman MW, and Santerre JP. Biomaterials 2000;21:1235-1246.
88. Baron A, Rodriguez-Hernandez J, Ibarboure E, Derail C, and Papon E. Int J Adhes Adhes 2009;29:1-8.
89. Gisselfalt K, Edberg B, and Flodin P. Biomacromolecules 2002;3:951-958.
90. Guan JJ and Wagner WR. Biomacromolecules 2005;6:2833-2842.
91. Yu HJ, Wang WS, Chen XS, Deng C, and Jing XB. Biopolym 2006;83:233-242.
92. Liu L, Wang YS, Shen XF, and Fang Y. Biopolym 2005;78:163-170.
93. Liu L, Li YE, Fang Y, and Chen LX. Carbohyd Polym 2005;60:351-356.
94. Duan KR, Chen HL, Huang J, Yu JH, Liu SY, Wang DX, and Li YP. Carbohyd Polym 2010;80(2):498-503.

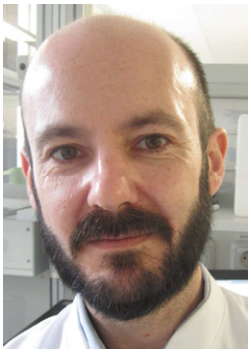
95. Lu YY, Liu L, and Guo SR. Biopolym 2007;86:403-408.
96. Huang Y, Li L, and Fang Ye. J Mater Sci Mater Med 2010;21:557-565.
97. Chen L, Ni YS, Bian XC, Qiu XY, Zhuang XL, Chen XS, and Jing XB. Carbohyd Polym 2005;60:103-109.
98. Sugih AK, Picchioni F, Janssen L, and Heeres HJ. Carbohyd Polym 2009;77:267-275.
99. Barikani M and Mohammadi M. Carbohyd Polym 2007;68:773-780.
100. Seiffert S and Sprakel J. Chem Soc Rev 2012;41:909-930.
101. Bender JL, Corbin PS, Fraser CL, Metcalf DH, Richardson FS, Thomas EL, and Urbas AM. J Am Chem Soc 2002;124:8526-8527.
102. Hoogenboom R, Moore BC, and Schubert US. Chem Commun 2006;38:4010-4012.
103. Nawaby AV, Farah AA, Liao X, Pietro WJ, and Day M. Biomacromolecules 2005;6:2458-2461.
104. Fustin CA, Guillet P, Schubert US, and Gohy JF. Adv Mater 2007;19:1665-1673.
105. Luo HY, Meng XW, Cheng C, Dong ZQ, Zhang S, and Li BJ. J Phys Chem B 2010;114:4739-4745.
106. Shuai XT, Merdan T, Unger F, and Kissel T. Bioconj Chem 2005;16:322-329.
107. Wu DQ, Wang T, Lu B, Xu XD, Cheng SX, Jiang XJ, Zhang XZ, and Zhuo RX. Langmuir 2008;24:10306-10312.
108. Dai XH, Dong CM, Fa HB, Yan DY, and Wei Y. Biomacromolecules 2006;7:3527-3533.
109. Wisse E, Spiering AJH, van Leeuwen ENM, Renken RAE, Dankers PYW, Brouwer LA, van Luyn MJA, Harmsen MC, Sommerdijk N, and Meijer EW. Biomacromolecules 2006;7:3385-3395.
110. van Beek DJM, Gillissen MAJ, van As BAC, Palmans ARA, and Sijbesma RP. Macromolecules 2007;40:6340-6348.
111. Wietor JL, van Beek DJM, Peters GW, Mendes E, and Sijbesmat RP. Macromolecules 2011;44(5):1211-1219.
112. Kim BS, Park SW, and Hammond PT. ACS Nano 2008;2:386-392.
113. Cameron DJA and Shaver MP. Chem Soc Rev 2011;40:1761-1776.
114. Choi J, Kim IK, and Kwak SY. Polymer 2005;46:9725-9735.
115. Wang JL and Dong CM. Polymer 2006;47:3218-3228.
116. Xie WY, Jiang N, and Gan ZH. Macromol Biosci 2008;8:775-784.
117. Wang JL, Wang L, and Dong CM. J Polym Sci Part A Polym Chem 2005;43:5449-5457.
118. Lang MD, Wong RP, and Chu CC. J Polym Sci Part A Polym Chem 2002;40:1127-1141.
119. Celik A, Kemikli N, Ozturk R, Muftuoglu AE, and Yilmaz F. React Funct Polym 2009;69:705-713.
120. Cui YJ, Ma XM, Tang XZ, and Luo YP. Eur Polym J 2004;40:299-305.
121. Yuan WZ, Yuan JY, Huang XB, and Tang XZ. J Appl Polym Sci 2007;104:2310-2317.
122. Wu RZ, Al-Azemi TF, and Bisht KS. Chem Commun 2009;14:1822-1824.
123. Gou PF, Zhu WP, Xu N, and Shen ZQ. J Polym Sci Part A Polym Chem 2008;46:6455-6465.
124. Xu JW and Shi WF. Polymer 2006;47:5161-5173.
125. Chan SC, Kuo SW, and Chang FC. Macromolecules 2005;38:3099-3107.
126. Hecht S, Ihre H, and Frechet JMJ. J Am Chem Soc 1999;121:9239-9240.
127. Hecht S, Vladimirov N, and Frechet JMJ. J Am Chem Soc 2001;123:18-25.
128. Smet M, Gottschalk C, Skaria S, and Frey H. Macromol Chem Phys 2005;206:2421-2428.

129. Meier MAR, Gohy JF, Fustin CA, and Schubert US. J Am Chem Soc 2004;126:11517-11521.
130. Joncheray TJ, Denoncourt KM, Mathieu C, Meier MAR, Schubert US, and Duran RS. Langmuir 2006;22:9264-9271.
131. Burgath A, Sunder A, Neuner I, Mulhaupt R, and Frey H. Macromol Chem Phys 2000;201:792-797.
132. Ding XY, Liu HW, Shi WF, and Skrifvars M. J of Appl Polym Sci 2009;112:1209-1214.
133. Hans M, Gasteier P, Keul H, and Moeller M. Macromolecules 2006;39:3184-3193.
134. Cao PF, Xiang R, Liu XY, Zhang CX, Cheng F, and Chen Y. J Polym Sci Part A Polym Chem 2009;47:5184-5193.
135. Lin Y, Liu XH, Dong ZM, Li BX, Chen XS, and Li YS. Biomacromolecules 2008;9:2629-2636.
136. Yang Z, Liu JH, Huang ZP, and Shi WF. Eur Polym J 2007;43:2298-2307.
137. Yang Z, Xie JD, Zhou W, and Shi WF. Journal of Biomed Mater Res Part A 2009;89A:988-1000.
138. Wang F, Bronich TK, Kabanov AV, Rauh RD, and Roovers J. Bioconj Chem 2005;16:397-405.
139. Lorenzo AT, Muller AJ, Lin MC, Chen HL, Jeng US, Priftis D, Pitsikalis M, and Hadjichristidis N. Macromolecules 2009;42:8353-8364.
140. Heise A, Trollsas M, Magbitang T, Hedrick JL, Frank CW, and Miller RD. Macromolecules 2001;34:2798-2804.
141. Tunca U, Ozyurek Z, Erdogan T, and Hizal G. J Polym Sci Part A Polym Chem 2004;42:4228-4236.
142. Yuan YY, Wang YC, Du JZ, and Wang J. Macromolecules 2008;41:8620-8625.
143. Saito N, Liu C, Lodge TP, and Hillmyer MA. Macromolecules 2008;41:8815-8822.
144. Altintas O, Hizal G, and Tunca U. Des Monomers Polym 2009;12:83-98.
145. Yang LP, Zhou HX, Shi GY, Wang Y, and Pan CY. J Polym Sci Part A Polym Chem 2008;46:6641-6653.
146. Chen WQ, Wei H, Li SL, Feng J, Nie J, Zhang XZ, and Zhuo RX. Polymer 2008;49:3965-3972.
147. Miura Y, Dote H, Kubonishi H, Fukuda K, and Saka T. J Polym Sci Part A Polym Chem 2007;45:1159-1169.
148. Gou PF, Zhu WP, and Shen ZQ. Biomacromolecules 2010;11:934-943.
149. Wang HB, Chen XS, and Pan CY. J Polym Sci Part A Polym Chem 2008;46:1388-1401.
150. Du JZ and Chen YM. Macromolecules 2004;37:3588-3594.
151. Wiltshire JT and Qiao GG. Macromolecules 2006;39:9018-9027.
152. Kweon H, Yoo MK, Park IK, Kim TH, Lee HC, Lee HS, Oh JS, Akaike T, and Cho CS. Biomater 2003;24:801-808.
153. Busby W, Cameron NR, and Jahoda CAB. Biomacromolecules 2001;2:154-164.
154. Pereira IHL, Ayres E, Patricio PS, Goes AM, Gomide VS, Junior EP, and Orefice RL. Acta Biomater 2010;6:3056-3066.
155. Lendlein A, Schmidt AM, Schroeter M, and Langer R. J Polym Sci Part A Polym Chem 2005;43:1369-1381.
156. Lendlein A, Schmidt AM, and Langer R. Proc Natl Acad Sci USA 2001;98:842-847.
157. Kelch S, Steuer S, Schmidt AM, and Lendlein A. Biomacromolecules 2007;8:1018-1027.
158. Wischke C, Neffe AT, Steuer S, Engelhardt E, and Lendlein A. Macromol Biosci 2010;10:1063-1072.
159. Zotzmann J, Behl M, Hofmann D, and Lendlein A. Adv Mater 2010;22:3424-3429.

160. Zotzmann J, Behl M, Feng YK, and Lendlein A. Adv Funct Mater 2010;20:3583-3594.
161. Jabbari E, Wang SF, Lu LC, Gruetzmacher JA, Ameenuddin S, Hefferan TE, Currier BL, Windebank AJ, and Yaszemski MJ. Biomacromolecules 2005;6:2503-2511.
162. Sharifi S, Mirzadeh H, Imani M, Ziaee F, Tajabadi M, Jamshidi A, and Atai M. Polym Adv Technol 2008;19:1828-1838.
163. Wu DQ, Zhang XZ, and Chu CC. J Biomater Sci Polym Ed 2003;14:777-802.
164. Turunen MPK, Korhonen H, Tuominen J, and Seppala JV. Polym Int 2002;51:92-100.
165. Bat E, Plantinga JA, Harmsen MC, van Luyn MJA, Zhang Z, Grijpma DW, and Feijen J. Biomacromolecules 2008;9:3208-3215.
166. Cho CS, Han SY, Ha JH, Kim SH, and Lim DY. Int J Pharm 1999;181:235-242.
167. Fay F, Linossier I, Langlois V, and Vallee-Rehel K. Biomacromolecules 2007;8:1751-1758.
168. Sahoo S, Sasmal A, Nanda R, Phani AR, and Nayak PL. Carbohyd Polym 2010;79:106-113.
169. Lemmouchi Y, Schacht E, and Lootens C. J Contr Rel 1998;55:79-85.
170. Turunen MPK, Laurila T, and Kivilahti JK. J Appl Polym Sci 2006;101:3677-3688.
171. Coccoli V, Luciani A, Orsi S, Guarino V, Causa F, and Netti PA. J Mater Sci Mater M 2008;19:1703-1711.
172. Campos E, Cordeiro R, Alves P, Rasteiro MG, and Gil MH. J Microencapsul 2008;25:154-169.
173. Benoit MA, Baras B, and Gillard J. Int J Pharm 1999;184:73-84.
174. Gutierrez-Pauls L, Gonzalez-Alvarez I, Barone ML, Gil-Alegre ME, and Torres-Suarez AI. Pharmazie 2007;62:864-868.
175. Shah LK and Amiji MM. Pharm Res 2006;23:2638-2645.
176. Jeong JC, Lee J, and Cho K. J Contr Rel 2003;92:249-258.
177. Slomkowski S. Polyester nano and microparticles by polymerization and by self assembly of macromolecules. In: Kumar R, Tabata Y, and Domb A, editors. Nanoparticles for Pharmaceutical Applications. Stevenson Ranch, Cal.: American Scientific Publisher, 2007. Chapter 16, pp. 288-303.
178. Ahmed F and Discher DE. J Contr Rel 2004;96:37-53.
179. Allen C, Han JN, Yu YS, Maysinger D, and Eisenberg A. J Contr Rel 2000;63:275-286.
180. Aliabadi HM, Mahmud A, Sharifabadi AD, and Lavasanifar A. J Contr Rel 2005;104:301-311.
181. Kim HJ, Kim TH, Kang KC, Pyo HB, and Jeong HH. Int J Cosmet Sci 2010;32:185-191.
182. Park EK, Kim SY, Lee SB, and Lee YM. J Contr Rel 2005;109:158-168.
183. Hu Y, Jiang ZP, Chen R, Wu W, and Jiang XQ. Biomacromolecules 2010;11:481-488.
184. Quaglia F, Ostacolo L, De Rosa G, La Rotonda MI, Ammendola M, Nese G, Maglio G, Palumbo R, and Vauthier C. Int J Pharm 2006;324:56-66.
185. Balmayor ER, Tuzlakoglu K, Azevedo HS, and Reis RL. Acta Biomater 2009;5:1035-1045.
186. Geng Y and Discher DE. J Am Chem Soc 2005;127:12780-12781.
187. Cai SS, Vijayan K, Cheng D, Lima EM, and Discher DE. Pharm Res 2007;24:2099-2109.
188. Kim SY, Shin ILG, Lee YM, Cho CS, and Sung YK. J Contr Rel 1998;51:13-22.
189. Duncan R. Nat Rev Drug Discov 2003;2:347-360.
190. Gros L, Ringsdorf H, and Schupp H. Angew Chem Int Ed 1981;20:305-325.
191. Allen C, Yu YS, Maysinger D, and Eisenberg A. Bioconj Chem 1998;9:564-572.

192. Duan KR, Zhang XL, Tang XX, Yu JH, Liu SY, Wang DX, Li YP, and Huang J. Colloid Surface B 2010;76:475-482.
193. Du JZ, Chen DP, Wang YC, Xiao CS, Lu YJ, Wang J, and Zhang GZ. Biomacromolecules 2006;7:1898-1903.
194. Azzam T and Eisenberg A. Langmuir 2007;23:2126-2132.
195. Gong CY, Shi S, Wang XH, Wang YJ, Fu SZ, Dong PW, Chen LJ, Zhao X, Wei YQ, and Qian ZY. J Phys Chem B 2009;113:10183-10188.
196. Sheikh FA, Barakat NAM, Kanjwal MA, Aryal S, Khil MS, and Kim HY. J Mater Sci Mater M 2009;20:821-831.
197. Kim BK, Hwang SJ, Park JB, and Park HJ. J Microencapsul 2005;22:193-203.
198. Slomkowski S. Ring-Opening Dispersion Polymerization. In: Matyjaszewski K and Moeller M, editors. Polymer Science: A Comprehensive Reference, vol. 4. Amsterdam: Elsevier, 2012. pp. 645-660.
199. Lemoine D, Francois C, Kedzierewicz F, Preat W, Hoffman M, and Maincent P. Biomater 1996;17:2191-2197.
200. Lemarchand C, Couvreur P, Besnard M, Costantini D, and Gref R. Pharm Res 2003;20:1284-1292.
201. Wang SB, Guo SR, and Cheng L. Int J Pharm 2008;350:130-137.
202. Calvo P, Sanchez A, Martinez J, Lopez MI, Calonge M, Pastor JC, and Alonso MJ. Pharm Res 1996;13:311-315.
203. Cauchetier E, Deniau M, Fessi H, Astier A, and Paul M. Int J Pharm 2003;250:273-281.
204. Espuelas MS, Legrand P, Loiseau PM, Bories C, Barratt G, and Irache JM. J Drug Target 2002;10:593-599.
205. Jiao YY, Ubrich N, Hoffart V, Marchand-Arvier M, Vigneron C, Hoffman M, and Maincent P. Drug Dev Ind Pharm 2002;28:1033-1041.
206. Hamoudeh M and Fessi H. J Colloid Interf Sci 2006;300:584-590.
207. Karatas A, Sonakin O, Kilicarslan M, and Baykara T. J Microencapsul 2009;26:63-74.
208. Jang JS, Kim SY, Lee SB, Kim KO, Han JS, and Lee YM. J Contr Rel 2006;113:173-182.
209. Elvira C, Fanovich A, Fernandez M, Fraile J, San Roman J, and Domingo C. J of Contr Rel 2004;99:231-240.
210. Ghaderi R, Artursson P, and Carlfors J. Pharm Res 1999;16:676-681.
211. Busby AJ, Zhang JX, Roberts CJ, Lester E, and Howdle SM. Adv Mater 2005;17:364-367.
212. Lee J, Oh S, Joo MK, and Jeong B. J Phys Chem Solids 2008;69:1596-1599.
213. Ajami-Henriquez D, Rodriguez M, Sabino M, Castillo RV, Muller AJ, Boschetti-de-Fierro A, Abetz C, Abetz V, and Dubois P. J Biomed Mater Res Part A 2008;87A:405-417.
214. Scharnagl N, Lee S, Hiebl B, Sisson A, and Lendlein A. J Mater Chem 2010;20:8789-8802.
215. Little U, Buchanan F, Harkin-Jones E, Graham B, Fox B, Boyd A, Meenan B, and Dickson G. Acta Biomater 2009;5:2025-2032.
216. Dikic T, Ming W, Thune PC, Van Benthem R, and De With G. J Polym Sci Part A Polym Chem 2008;46:218-227.
217. Rouxhet L, Duhoux F, Borecky O, Legras R, and Schneider YJ. J Biomater Sci Polym Ed 1998;9:1279-1304.
218. Sasmazel HT, Manolache S, and Guemuesderelioglu M. J Biomater Sci Polym Ed 2009;20:1137-1162.
219. Zhu YB and Sun Y. Colloid Surface B 2004;36:49-55.
220. Feng J, Gao CY, and Shen JC. Chem Mater 2004;16:1319-1322.

221. Causa F, Battista E, Della Moglie R, Guarnieri D, Iannone M, and Netti PA. Langmuir 2010;26:9875-9884.
222. Prime EL, Hamid ZAA, Cooper-White JJ, and Qiao GG. Biomacromolecules 2007;8:2416-2421.
223. Hui S, Wirsen A, and Albertsson AC. Biomacromolecules 2004;5:2275-2280.
224. Zhu YB, Gao CY, and Shen JC. Biomater 2002;23:4889-4895.
225. Edlund U, Danmark S, and Albertsson AC. Biomacromolecules 2008;9:901-905.
226. Xu FJ, Wang ZH, and Yang WT. Biomater 2010;31:3139-3147.
227. Behl M and Lendlein A. Mater Today 2007;10:20-28.
228. Behl M, Razzaq MY, and Lendlein A. Adv Mater 2010;22:3388-3410.
229. Ping P, Wang WS, Chen XS, and Jing XB. Biomacromolecules 2005;6:587-592.
230. Nagahama K, Ueda Y, Ouchi T, and Ohya Y. Biomacromolecules 2009;10:1789-1794.
231. Mya KY, Gose HB, Pretsch T, Bothe M, and He CB. J Mater Chem 2011;21:4827-4836.
232. Nagata M and Sato Y. J Polym Sci Part A Polym Chem 2005;43:2426-2439.
233. Nagata M and Kitazima I. Colloid Polym Sci 2006;284:380-386.
234. Nagata M and Inaki K. J Appl Polym Sci 2011;120:3556-3564.
235. Chang YW, Eom JP, Kim JG, Kim HT, and Kim DK. J Ind Eng Chem 2010;16:256-260.
236. Zhu GM, Xu SG, Wang JH, and Zhang LB. Radiat Phys Chem 2006;75:443-448.
237. Luo HY, Liu Y, Yu ZJ, Zhang S, and Li BJ. Biomacromolecules 2008;9:2573-2577.



Adam Sisson received his Ph.D. in supramolecular chemistry from the University of Bristol, UK. He then conducted postdoctoral research at the University of Geneva, Switzerland and the Free University Berlin, Germany, investigating applications of self-assembled and polymeric nanoscale chemical architectures. Since 2009 he is Junior Group Leader in Cell and Tissue Specific Materials at the Institute of Biomaterial Science at Helmholtz-Zentrum Geesthacht in Teltow and the Berlin-Brandenburg Centre for Regenerative Therapies, Germany. Research interests lie in manipulating the interactions of biological species with synthetic polymeric architectures on varied length scales.

Duygu Ekinci is pursuing her Ph.D. at the Institute of Biomaterial Science at Helmholtz-Zentrum Geesthacht in Teltow, Germany under the supervision of Prof. Andreas Lendlein. She received her M.Sc. degree in Advanced Materials and Engineering from the University of Ulm, Germany, in 2009. Her current research interest focuses on the synthesis and biomedical applications of polyether hydrogels.

Andreas Lendlein is the Director of the Institute of Biomaterial Science at Helmholtz-Zentrum Geesthacht in Teltow, Germany and Member of the Board of Directors of the Berlin-Brandenburg Centre for Regenerative Therapies. He is a professor at the University Potsdam and Honorary Professor at Freie Universität Berlin as well as Member of the Medical Faculty of Charité University Medicine Berlin. He completed his Habilitation in Macromolecular Chemistry in 2002 at RWTH Aachen University and received his doctoral degree in Materials

Science from the Swiss Federal Institute of Technology (ETH) in Zürich. His current research interests include (multi)functional polymer-based materials, biomaterials and their interaction with biological environments as well as the development of medical devices and controlled drug delivery systems especially for regenerative therapies.