General Synthesis Methods of Poly (ε-caprolactone)-Based Graft Copolymers

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Synthetic biopolymers are attractive alternatives to biobased polymers, especially because they rarely induce an immune response in a living organism. Poly ε-caprolactone (PCL) is a well-known synthetic aliphatic polyester universally used for many applications, including biomedical and environmental ones. To expand the range of applications for PCL, researchers have investigated the possibility of grafting polymer chains onto the PCL backbone. As the PCL backbone is not functionalized, it must be first functionalized in order to be able to graft reactive groups onto the PCL chain. These reactive groups will then allow the grafting of new reagents and especially new polymer chains. Grafting of polymer chains is mainly carried out by “grafting from” or “grafting onto” methods.

Keywords: poly ε-caprolactone ; graft copolymers ; biodegradability ; backbone functionalization

1. Synthesis of a Functionalized Caprolactone

Copolymerization of a functionalized caprolactone (CL) with a native CL is probably the most common method giving access to new functionalized poly ε-caprolactone (PCL)-based graft (co)polyesters. Functionalized CLs are the starting points for PCL-based graft copolymers, whose properties depend on the nature and proportion of functionalized CL in the copolymer. Many functionalized CLs are described in the literature: carboxyl-PCL [1][2], hydroxyl-PCL [1][3], amino-PCL [4][5][6][7][8][9], chloro-PCL [4][9], azido-PCL [4][9], propargyl-PCL [7][8], iodo-PCL [10], bromo-PCL and keto-PCL [11], 2-bromo-2-methylpropionyl-PCL [12], γ-(triethylsilyloxy)-PCL and γ-ethylene ketal-PCL [13], benzyloxy-PCL [14], 2-hydroxyethyl-PCL [15], and isocyanate-PCL [16]. Some of these functionalized copolymers are mentioned in a chapter of a book [17] and a review [18]. However, this versatile copolymerization approach has some drawbacks. Most of functionalized CLs are not commercially available; it is mandatory to synthesize and purify these lactones rigorously before polymerization, which is sometimes a challenging task. This is time consuming and involves multi-step chemical reactions with rather low yields. As a result, the overall yield of the synthesis is low, so the functionalized CL is quite expensive. On the other hand, several functional groups (e.g., epoxides, alcohols, or carboxylic acids) are not compatible with initiators such as aluminum and tin(IV) alkoxides frequently used for ring-opening (co)polymerization (ROP) of functionalized CLs. Although this drawback can be overcome by protecting the functional groups, the protecting groups must be removed after polymerization, which results in partial degradation of the polymer chain, especially when acidic conditions are required [17]. Moreover, the ROP of substituted CLs gives polymers with rather low polymerization degrees [6][7].

It is worth mentioning that some functionalized PCL can also be obtained by copolymerization of cyclic ketene acetals (CKA) with vinyl compounds, in particular vinyl ethers (VE) [19][20][21]. However, in these cases the backbone is not strictly PCL but a copolymer P(CKA-*co*-VE) of which only a part is PCL whose structure is not substituted.

In any case, in the literature very few of these functions are then used as anchor points for the grafting of polymer segments and therefore they do not give rise to graft copolymers.

2. PCL Backbone Modification

Along with the copolymerization method, post-modification of the PCL backbone is described. Basically, post-modifications of the PCL chain to yield a functionalized PCL do not involve the synthesis of a functional monomer. Therefore, the main advantages of post-modification over the functionalized monomers syntheses are ease, rapidity, and versatility. However, post-modification of polyesters chains, especially PCL, is quite difficult given the lack of reactive functions on their chains and the possible hydrolysis of ester groups during the post-modification reaction.

2.1. Anionic Modification

Probably the most powerful method for functionalizing the PCL chain, described primarily in 2000, is the anionic chemical modification of PCL [22]. This method gives access to a multitude of substituted PCLs [5][6][16][23][24][25][26][27][28]. This direct post-polymerization method is based on a two-step one-pot anionic reaction in α-position of the carbonyl of PCL.

The main characteristics of this method were described by Ponsart et al. [22]. Compared to the copolymerization of a functionalized caprolactone, the main advantages are the short reaction time, the functionalized PCL being obtained in one day, and the numerous possible substitutions. On the other hand, it appears that the main drawbacks of this method are (i) the breaking of some ester bonds in the PCL chain especially in the first step of the reaction, leading to a decrease in molar masses and (ii) the rather low substitution degree, typically under 20%, which has been attributed to the steric hindrance of the macropolycarbanion. However, the polymerization degree of the functionalized PCL obtained by this method is equivalent to that obtained by copolymerization of a substituted caprolactone with genuine caprolactone [6]. To increase the substitution degree, a higher ratio (LDA)/(monomer) is required, but the higher this ratio, the higher the proportion of chain breakings. Therefore, this ratio cannot be increased if a high molar mass is desired. The two parameters, substitution degree and molar mass, are correlated.

2.2. Surface Modification

An advantage of the post-polymerization modification technique is that it can be applied to the surface modification of a manufactured object, without modifying the shape and the main properties (mechanical properties, degradation properties etc.) of the object. This is of particular interest when only surface properties need to be modified, especially in the biomedical field to improve the biocompatibility of particles or implantable devices and to promote endothelial cells adhesion and growth.

Some specific methods are well known to chemically modify the surface of a PCL-based device, including surface hydrolysis, aminolysis, and UV or plasma treatment. In general, polymer grafting is carried out in two steps: the first is the functionalization of the PCL surface and the second involves the polymerization of a monomer initiated by the new surface functions.

Hydrolysis in a basic medium is the most conventional method to functionalize a PCL surface. It results in formation of carboxylates and hydroxyl groups on the device surface [29]. The modification is studied as a function of hydrolysis time, temperature, and alkaline concentration with the aim of promoting endothelial cell (EC) adhesion and growth [30]. PCL films are subjected to variations in hydrolysis degrees using different pretreatment solutions to introduce various densities of carboxylate/hydroxyl groups onto the surfaces to modulate surface wettability and surface roughness. The hydroxyl groups on the hydrolyzed surface of a PCL film are reacted with 2-bromo isobutyrate bromide to prepare brominated PCL, which can initiate atom transfer radical polymerization (ATRP) of glycidyl methacrylate (GMA) to give PCL-*g*-PGMA [31]. The reactive epoxide groups of the grafted PGMA brushes were used for the direct coupling of cell-adhesive collagen and Arg-Gly-Asp-Ser (RGDS) peptides to improve the cell-adhesion properties of the PCL film.

Aminolysis is also used to functionalize the surface of PCL devices. Xiong et al. used 1,6 hexane diamine to obtain an aminated PCL, which then reacts with 2-bromoisobutyrate bromide to give an ATRP surface initiator for the polymerization of glycidyl methacrylate (GMA). Epoxy rings of the PCL-*g*-P(GMA) obtained can then react with gelatin to bind this compound to the PCL surface [32]. A drastic increase in hydrophilicity is observed, as well as improved endothelial cells attachment and proliferation. An anti-thrombogenic profile was also observed.

However, strictly speaking, there is no chemical modification of the PCL chain upon hydrolysis or aminolysis, but chain breakings with the formation of carboxylates/hydroxyl/amine functions at the chain ends. Therefore, these copolymers are not real PCL-based graft copolymers.

Some authors have described the surface modification of PCL to attach growth factor or cell-adhesive biomolecules by UV photo-initiation [33]. A vapor phase is sometimes used for UV grafting [34][35]. UV-photoinduction was also used to graft poly gallic acid onto a previously hydrolyzed surface of PCL films to inhibit oxidative stress in epithelial cells [36]. Zhu et al. achieved grafting of poly methacrylic acid by the photo-oxidation of a PCL surface with hydrogen peroxide followed by UV irradiation at 30 °C of methacrylic acid [37]. The objective was also to immobilize gelatin on the surface to increase the surface cytocompatibility.

Plasma treatment is another method in the chemical modification of a polymer surface [38]. The surface modification depends on the gas (argon, oxygen, hydrogen peroxide, carbon dioxide, ammoniac), plasma power and exposure time

[39]. Plasma treatment is widely described as a clean and environmentally friendly technique to improve the hydrophilicity, biocompatibility and biological performance of polymers for biomedical and tissue engineering applications [40][41]. Han et al. showed that on a PCL surface treated with argon plasma, human dermal fibroblast (nHDF) cell attachment density increased 60-fold after 1 min of treatment and more than 100-fold after 4 h of seeding compared to untreated PCL [42]. Oxygen plasma treatment allowed the grafting of polyethylene glycol mono acrylate onto a PCL membrane to prevent biofouling. The presence of grafted PEG on the surface was demonstrated by XPS technique and by a variation of the contact angle from 107° to 43°. PEG grafting led to a drastic reduction in fibroblasts adhesion. Oxygen plasma was also used to treat PCL electrospun nanofibers to allow initiation of graft copolymerization of acrylamide monomers [43]. The authors note an improvement in the antithrombogenicity of the grafted surface. The presence of hydrophilic functional groups was demonstrated by ATR-FTIR and contact angle measurements. Similarly, gamma irradiation of a PCL surface induced stepwise graft polymerization of acrylic acid (AA) and 2-aminoethyl methacrylate hydrochloride (AEMA) [44].

2.3. Reactive Extrusion

Reactive groups such as maleic anhydride are grafted onto the PCL chain by reactive extrusion in the presence of dicumyl peroxide as initiator, leading to possible formation of PCL-based graft copolymers [45]. However, in general, reactive extrusion requires drastic experimental conditions, is often not or poorly controlled and is not applicable to many chemical reactions.

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