ARS Pharmaceutica
ISSN: 0004-2927
http://farmacia.ugr.es/ars/

ARTÍCULO DE REVISIÓN

Drug delivery systems based on poly(ε-caprolactone) for cancer treatment

Sistemas transportadores de fármacos basados en el polímero poly(ε-caprolactona) para el tratamiento del cáncer.

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ABSTRACT

Chemotherapy agents have little or no specificity over cancer cells, resulting in low therapeutic concentrations at the tumor site (a consequence of a broad systemic distribution), and severe side effects. With the aim of avoiding cancer therapy failure, several approaches such as design of new anticancer drugs, chemical engineering of conventional drugs and development of drug delivery systems have been proposed. The objective is to enhance drug localization at the tumor region (by controlling its biodistribution profile) and, therefore, to increase the anti-tumor efficacy (even in multi-drug resistant tumors), while reducing systemic side effects. One of the most promising approaches to the problem is the development of drug nanocarriers based on the polymer poly(ε-caprolactone). In this review we will focus our attention on these polymeric colloids, particularly on the most significant characteristics and formulation procedures, and on their use as nanoplatforms for the delivery of chemotherapy agents to the tumor site. Furthermore, the most recent *in vitro* and *in vivo* investigations on the subject are extensively reviewed.

KEYWORDS: Anti-tumor Drug, Cancer, Controlled Release, Drug Carriers, Drug Delivery, Polymeric Particles, Poly(ε-caprolactone).

INTRODUCCION

Cancer therapy strategies are currently focussed on surgery, chemotherapy, radiotherapy, immunotherapy and hormonal therapy. These conventional strategies are limited by the accessibility to the tumor and the lack of selectivity towards tumor cells, the spread of cancer cells throughout the body, and the risk of operating on a vital organ. Regarding cancer chemotherapy, treatment failure is frequently encountered even in the most sensitive cancers to chemotherapy agents[1]. Several reasons have been pointed out for chemotherapy failure: *i*)

Fecha de Recepción (Date received): 03/07/09
Fecha de Aceptación (Date accepted): 20/09/09
Ars Pharm, 2009, Vol.50 nº2; 83-96.

the physicochemical properties of many drugs, e.g., hydrophobicity, promotes the unsuccessful localization at the cancer site; *ii*) the unfavorable pharmacokinetics (rapid clearance and rapid *in vivo* degradation) determine the need of higher doses and rigorous treatment schedules to obtain a therapeutic effect; *iii*) the relative poor selectivity of chemotherapy agents for targeted tumor cells; *iv*) the large biodistribution and non-intended extravasation with severe side effects in non-targeted sites; and *v*) the susceptibility to induce drug resistance[2-4]. Cancer physiology is also responsible for the chemotherapy failure, mainly because of the absence of a non-functional lymphatic system that allows drug escaping out of the tumor, and due to a very high hydrostatic pressure gradient inside the tumor that difficult a uniform drug diffusion inside the tumor[5,6].

The association of anti-tumor drugs to colloidal delivery systems in cancer treatment has been proposed to improve their efficacy and to reduce their associated toxicity. This strategy could allow obtaining a specific accumulation at the tumor site, an improvement of the pharmacokinetic profile, a prolongation of the exposure of the tumor cells to these active agents and a minimization of the severe side effects[2,7].

With this aim, it have been established that a suitable anti-tumor drug delivery system should have the following properties: *i*) small size (≤ 500 nm) to allow a large biodistribution and an adequate perfusion at the target site; *ii*) the ability to deliver therapeutic drug quantities, without overloading the organism with foreign material; *iii*) physical stability and low drug leakage problems under storage and *in vivo*; *iv*) controlled drug release rates exclusively at the targeted tumor; and *v*) maximum biocompatibility and biodegradability (with very low toxicity of breakdown products), and minimal antigenicity[2,8]. These drug carriers are frequently based on vesicular (liposomes and niosomes) and polymeric systems. Special approaches such as surface-functionalization (e.g., with specific ligands to tumor cells) and engineering of stimuli-sensitive materials, could enhance the biodistribution profile of loaded drugs and, thus, resulted in a more efficient tumor therapy[2,6,9].

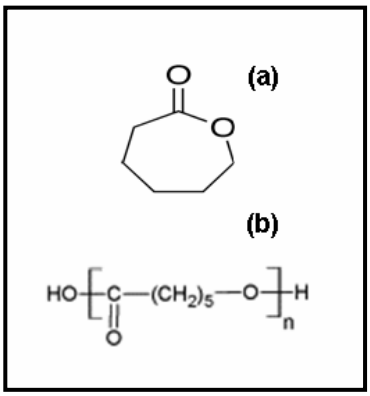
One of the most promising materials for the design of nanocarriers loaded with chemotherapy agents is the biodegradable polymer poly(ε-caprolactone) (PCL). This aliphatic polyester is very suitable for controlled drug delivery due to its high permeability to many drugs and non-toxicity, its exceptional ability to form blends with other polymers, and its very low degradation rate (compared to other well known drug carriers, such as poly(D,L-lactide-*co*-glycolide) (PLGA)[10]. Thus, it is of great interest to review the most significant characteristics and preparation procedures of PCL, giving special attention to its use in drug delivery to tumors. This paper will also detail the most important *in vitro* and *in vivo* investigations on the subject.

MAJOR PROPERTIES OF POLY(ε-CAPROLACTONE) FOR DRUG DELIVERY

ε-caprolactone (ε-CL) is a monomer widely used in the preparation of different polymers, including poly(ε-caprolactone) (PCL), by opening the with nucleophiles, e.g., water and alcohol. PCL is a synthetic aliphatic polyester, biodegradable, biocompatible and highly hydrophobic. It is typically prepared by ring-opening polymerization of ε-CL (figure 1). The

average molecular weight (M_w) of PCL may vary from 10000 to 42500 Da. PCL is graded according to this M_w. PCL is soluble at room temperature in chloroform, dichloromethane, carbon tetrachloride, benzene, toluene, cyclohexanone and 2-nitropropane. It has a low solubility in acetone, 2-butanone, ethyl acetate, and it is insoluble in alcohol, petroleum, ether and diethyl ether[11,12].

Figure 1. Chemical structure of (a) ε-caprolactone and (b) poly(ε-caprolactone).



This crystalline polymer has been widely utilized in numerous biomedical applications such as design of sustained-release drug delivery systems, because of its slow degradation rate, high drug permeability and non-toxicity. It is also used with very promising results in tissue-engineering scaffolds[11,12]. The combination of PCL with other polymers, such as PLGA or poly(D,L-lactide) (PLA), is widely used to obtain copolymers with higher stress crack resistance, dyeability and adhesion properties. The formulation of PCL-based copolymers can also allow manipulating the drug release rate from this systems[13,10].

In vivo studies have suggested the great biocompatibility, cytocompatibility and non-toxicity of PCL, with only non-significant inflammation reactions as a consequence of the high local concentrations assayed in these studies[14-16]. The degradation of PCL is an autocatalyzed process, whereby the generated carboxylic groups catalyze an autohydrolysis reaction, i.e. the cleavage of additional ester groups[14]. *In vivo* degradation is also clearly determined by phagocytosis[10].

SYNTHESIS PROCEDURES FOR THE FORMULATION OF DRUG-LOADED POLY(ε-CAPROLACTONE) CARRIERS

Poly(ε-caprolactone) (PCL) particles can be prepared either by the polymer alone or by using PCL copolymers or blends. Several methods have been reported in the literature for the preparation of drug-entrapped PCL particles, including interfacial disposition, interfacial polymerization, solvent evaporation, desolvation of macromolecules, emulsion polymerization in continuous aqueous phase or in continuous organic phase, or electrohydrodynamic atomization, to cite just a few[10].

With respect to drug-loaded PCL microparticles, the most important preparation methods are:

i) The o/w emulsion solvent extraction/evaporation method, where typically the required amount of polymer and drug are dissolved in an organic phase which is emulsified under mechanical stirring with a poly(vinyl alcohol) (PVA) solution to form an o/w emulsion[17].

ii) The w/o/w emulsion solvent evaporation technique. An aqueous solution of the drug is emulsified with PCL in dichloromethane. Then, the resulting w/o emulsion is again emulsified under mechanical stirring with water containing PVA as an emulsifier[18].

iii) The spray drying technique. An organic solution of the drug and the polymer is made in a mixture of dichloromethane and chloroform (1:1). This organic solution is finally sprayed through a nozzle in a spray-drier[19].

iv) The solution-enhanced dispersion method. This approach overcomes the problems associated to the use of organic solvents (e.g., toxicity). It is based on the use of supercritical fluids like carbon dioxide[20].

v) The hot melt technique. This synthesis method is frequently used for the preparation of polymeric microparticles with low melting point materials, such as PCL. The molten polymer is dispersed in a suitable dispersion medium and slowly cooled to form the microparticles[21].

Regarding the formulation of PCL nanoparticles, the interfacial polymer disposition and the dialysis methods are frequently used[10,22]. Interfacial polymer disposition is based on the displacement of a water-miscible semi-polar solvent from a lipophilic solution. Briefly, the polymer is dissolved in an organic solvent (e.g., acetone). A mixture of phospholipids is prepared in the same organic solvent by heating to near the boiling point. After mixing both solutions, the resulting organic phase is mixed with a benzyl benzoate-drug solution and it is poured under stirring to an aqueous poloxamer solution. A colloidal nanoparticle suspension is immediately obtained and the organic solvent is removed under reduced pressure. Regarding the dialysis method, the polymer is dissolved in an organic solvent (usually, dimethylformamide) and the drug is added to this solution under stirring at room temperature. After removing the organic solvent, dialysis is done using a cellulose membrane bag during 24 h. Subsequently, the micellar solution is collected from the bag, sonicated and centrifuged to eliminate the unloaded drug and the macroaggregates. Finally, lyophilization is carried out for 2 days, obtaining the polymeric nanoparticles.

The preparation procedures that are used for the formulation of PCL copolymers are usually based of the previously commented synthesis methods for the preparation of PCL micro- and nano-particles[10]. The synthesis routines that are mainly followed are the nanoprecipitacion method, the interfacial disposition technique, the solvent displacement process and the double emulsion pressure homogenization technique[10,23,24]. Following these preparation methods, it have been synthesized poly(ethylene oxide) (PEO)–poly(propylene oxide) (PPO)–poly(ethylene oxide)–PCL [PEO-PPO-PEO)–PCL], PEO-PCL[25], methoxy poly(ethylene glycol) (MePEG)–PCL[26], PCL–PEG–PCL [27,28] and self-assembled amphiphilic PCL grafted PVA (PCL-*g*-PVA) copolymers[29]. PCL nanoparticles have also been surface-functionalized with chitosan and poly-L-lysine[30].

APPLICATIONS OF POLY(ε-CAPROLACTONE) AS DRUG DELIVERY SYSTEMS FOR CANCER TREATMENT

Biodegradable poly(ε-caprolactone) (PCL) particles are one of the most promising drug delivery systems. Various categories of drugs have been encapsulated in PCL micro- and nano-particles for their effective delivery. The results that have been obtained *in vitro* and *in vivo* with anti-tumor drug-loaded PCL particles have determined their potential in cancer treatment. PCL colloids loaded with anticancer drugs (e.g., 5-fluorouracil, doxorubicin, paclitaxel, etc.) have shown enhanced anti-tumor activity as a consequence of a higher therapeutic efficacy and a reduced systemic toxicity[2,10]. The development of multi-drug resistances associated to long-term chemotherapy can also be minimized[31] or overcome[32].

Tamoxifen-loaded PCL nanoparticles were proposed for the treatment of breast cancer[31]. The preparation procedure is based on a solvent diffusion technique which involved the addition under stirring of a drug-polymer acetone solution into a pluronic® F-68 aqueous solution. Cell internalization studies in MCF-7 breast cancer cells employing fluorescent nanoparticles showed that after 1 hour of incubation, a high concentration of nanoparticles was found in the cytoplasm and in the perinuclear region, suggesting a great cell penetration (higher than in the case of the free drug) by a non-specific endocytosis[33]. Even more, surface functionalization with PEO significantly increased drug accumulation within tumor as well as extended their presence in the systemic circulation[34]. It was determined that the higher concentration of nanoparticles delivered to the tumor would result in net intracellular drug concentration and, hence, greater efficacy of the treatment. Hence, this tamoxifen-loaded nanocarrier was supposed to be very useful in effective drug delivery to breast cancer, which may be especially interesting to minimize the adverse side effects (e.g., subsequent endometrial cancer) and the development of resistances associated to long-term prophylactic therapy in high-risk and postmenopausal women.

A number of 5-fluorouracil (5-FU) delivery systems based on PCL have been studied for cancer treatment[35-37]. Recently, PCL particles loaded with doxifluridine (5´-deoxy-5-fluorouridine, 5´-DFUR) were prepared by ring-opening polymerization of ε-CL, using Sn(II) 2-ethylhexanoate ($Sn(Oct)_2$) as catalyst. This is a prodrug that is mostly converted to the active drug (5-FU) by the enzyme thymidine phosphorylase in tumor tissue[30]. Moreover, PCL colloids have been formulated for the enhancement of the bioavailability and *in vivo* stability of curcumin (a polyphenolic compound with anti-tumor activity) with very interesting results[38]. PCL particles have also been loaded with the anti-estrogen RU 58668 (a promising estrogen-dependent anticancer agent) (mean diameter ≈ 30 – 50 nm) and tested for cancer treatment. This formulation developed an intratumoral extravasation behavior and the slow drug release proved to be able to inhibit estrogen-induced transcription in human breast cancer cells[39].

One of the most interesting applications of PCL nanoparticles is as anti-tumor targeting systems in multi-drug resistance (MDR) tumors. As an example, a combination of paclitaxel (PTX) and C6-ceramide (CER, an apoptotic signalling molecule) in PCL nanoparticles (≈ 200 nm) surface functionalized with PEO was used for overcoming MDR in ovarian cancer[40]. A single dose of PTX (20 mg/Kg) and CER (100 mg/kg)-loaded nanoparticle formulations to

subcutaneous sensitive (wild-type) and MDR-1 positive SKOV-3 human ovarian adenocarcinoma xenograft-bearing female Nu/Nu mice, induced a significant ($P < 0.05$) tumor growth suppression as compared to the administration of aqueous solutions of each molecule. For instance, in SKOV-3 wild-type model, more than 4.3-fold increase ($P < 0.05$) in tumor growth delay and 3.6-fold ($P < 0.05$) increase in tumor volume doubling time (DT) were observed when co-administering both types of nanoparticles as compared to untreated animals. Similarly, 3-fold increase ($P < 0.05$) in tumor growth delay and tumor volume DT was observed in the SKOV-3_{TR} multi-drug resistance model. With respect to the toxicity, no significant differences were observed. Moreover, a paclitaxel/tamoxifen co-therapy based on PEO-PCL nanoparticles showed a decrease in the inhibitory concentration 50 (IC_{50}) of PTX by 10-fold in SKOV-3 cells and by > 3-fold in SKOV-3_{TR} cells, without any significant acute toxicity[32].

Depot-based PCL systems have been also proposed for cancer treatment with very promising results. As an example, a bleomycin depot based on PCL microparticles was evaluated *in vivo* in tumor-bearing mice. Interestingly, upon subcutaneous injection, the biodegradable depot-forming PCL microspheres controlled drug release and significantly suppressed the tumor growth kinetics compared to control[41]. An injectable PTX-polymer paste formulation based on a random copolymer of PLA and PCL with PEG, blended with MePEG was proposed for the treatment of prostate tumors. This PTX-loaded copolymer was administered intratumoraly into non-metastatic human prostate LNCaP tumor-bearing mice. The administration of this PTX-loaded paste induced a decrease in the serum prostate-specific antigen (PSA) levels and in the tumor volume in comparison to the blank paste. No significant toxicity but minor ulceration at the injection site was observed[42]. Finally, an injectable and *in situ* forming drug delivery system based on photocrosslinked poly(ε-caprolactone fumarate) networks loaded with tamoxifen citrate (TC) were evaluated against MCF-7 breast cancer cell line. The cytotoxicity assay showed that while this photocrosslinked network exhibited no significant cytotoxicity against MCF-7 cells, ≈ 60 % of the MCF-7 cells were killed after incubation with TC-loaded devices[43].

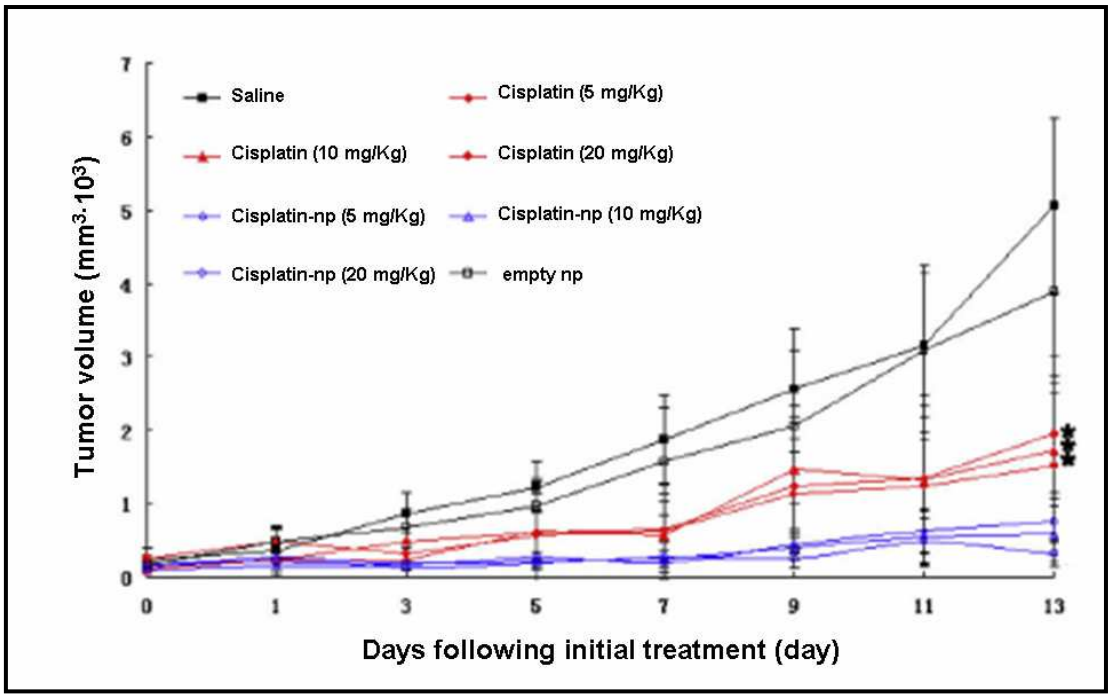
Furthermore, PCL micelles are emerging as effective drug carriers for hydrophobic photosensitizers in photodynamic therapy (PDT) and, even, as a potential dual carrier for the synergistic combination of PDT and chemotherapy for the treatment of cancer[44]. As an example, the photophysical and photochemical properties of protoporphyrin IX (PpIX)-loaded MePEG-*b*-PCL diblock copolymers (mean diameter ≈ 50 nm; loading efficiency ≈ 80 %) were compared to that of free PpIX. The cellular uptake of PpIX in RIF-1 cells using PpIX micelles was approximately two-fold higher than free PpIX. *In vitro* PDT results showed that the PpIX micelles have markedly increased photocytotoxicity over that achieved with free PpIX, by nearly an order of magnitude at the highest light dose used[45]. Micelles of MePEG750-*b*-oligo(ε-caprolactone)$_5$ (MePEG750-*b*-OCL_5) were loaded with the photosensitizer m-tetrahydroxyphenylchlorin (mTHPC) by a film hydration method. The cellular uptake of the drug-loaded micelles and their photocytotoxicity on human neck squamous carcinoma cells, in the absence and presence of lipase, were compared with free and liposomal mTHPC (Fospeg®) formulations. This *in vitro* study revealed that the high loading capacity of the micelles, the high stability above the critical aggregation concentration

and the lipase-induced release of the photosensitizer make them very promising carriers for PDT *in vivo*[46].

As can be concluded, taking into account these very interesting results, the potential of PCL particles loaded with anticancer drugs is evident. However, the majority of the research efforts have been focussed on the use of copolymers due to their better drug loading and release properties, and to a more suitable biodegradation profile[10]. As an example, MePEG/PCL amphiphilic block copolymers (nanoparticle diameter ≈ 100 nm) proved to be able to encapsulate doxorubicin (DOX) in aqueous solutions. Confocal laser scanning microscopy (CLSM) demonstrated that drug-loaded micelles accumulated mostly in cytoplasm instead of cell nuclei, in contrast to free DOX. Furthermore, these drug-loaded particles exhibited time-delayed cytotoxicity in human MCF-7 breast cancer cells[47]. This biodegradable block copolymer has also been surface-functionalized with folic acid to target a folate-binding protein that is overexpressed on the surface of many tumor cells. With this aim, PTX-loaded folate-conjugated MePEG/PCL micelles (50 – 130 nm) were prepared by micelle formation in aqueous medium. The *in vitro* PTX release profile from the micelles showed no initial burst release but a clear sustained release. Interestingly, these PTX-loaded micelles proved much higher cytotoxicity for cancer cells (e.g., MCF-7 and HeLa cells) than MePEG/PCL micelles non-conjugated to folate. A confocal image analysis revealed that fluorescent PTX-loaded folate-conjugated micelles were endocytosed into MCF-7 cells through the interaction with overexpressed folate receptors on the surface of cancer cells[48]. Furthermore, PEG/PCL nanoparticles were prepared by a dialysis method and further surface-functionalized with folate moieties (via a coupling reaction between the –OH groups of PEG and the –COOH group of folic acid) for the active targeting of 5-FU and PTX to tumors. It was observed an enhanced cytotoxicity of these drug-loaded nanoparticles against folate receptor expressing tumor cells[49]. MePEG/PCL nanoparticles loaded with taxol were prepared by a dialysis procedure[26]. This copolymer was also used in the vehiculization of geldanamycin. In this case, the pharmacokinetic profile of the drug was improved (enhancement in the AUC ≈ 72-fold) and this formulation exhibited a lower systemic toxicity[50]. Finally, MePEG/PCL nanoparticles loaded with cisplatin (entrapment efficiency ≥ 75 %) have shown a significant less toxicity and an enhanced circulation time, compared to the free drug. Cisplatin release occurred in a sustained manner. *In vitro* cytotoxicity studies proved the efficacy of cisplatin-loaded nanoparticles against BGC823 and H_{22} cancer cell lines in a dose and time-dependent manner. Furthermore, compared with the free drug, cisplatin-loaded nanoparticles exhibited a superior anti-tumor effect by delaying tumor growth when delivered intratumorally (figure 2)[51].

Figure 2. Tumor volume of established H_{22} xenografts in ICR mice during therapy under different treatments. Mice were intratumorally treated with different protocols on Day 0 (tumor volume: 100 mm^3). Saline: vehicle; empty np: empty nanoparticles; Cisplatin: free cisplatin at a dose of 5, 10 and 20 mg/kg, respectively; cisplatin-np: cisplatin-loaded nanoparticles in a saline solution at equivalent cisplatin doses of 5, 10 and 20 mg/kg, respectively. Data are presented as mean ± SD (n = 6). The difference between tumor volumes in the group of saline and cisplatin-loaded nanoparticles is highly significant ($P < 0.01$). A significant difference ($P < 0.05$) is also observed between the group of free cisplatin

and cisplatin-loaded nanoparticles at the equivalent dose (*). Reprinted with permission from Ref. [51]. Copyright Elsevier (2008).



Another PCL-based block copolymer was proposed for the delivery of vinblastine. By a modified o/w emulsion method PCL grafted dextran nanoparticles were prepared, and an *in vitro* cytotoxicity assay in a breast cancer cell line (MCF-7) showed higher cancer cell mortality than the free drug[52]. This drug delivery system was also successfully assayed *in vitro* with coumarin-6 in a human gastric cancer cell line (SNU-638)[53].

Poly(ethylene oxide)-*block*-poly(ε-caprolactone) (PEO-*b*-PCL) and poly(ethylene oxide)-*block*-poly(α-benzyl carboxylate ε-caprolactone) (PEO-*b*-PBCL) micelles (< 90 nm) were engineered by a co-solvent evaporation technique as nanocarriers for the delivery of cucurbitacin I and B, which are inhibitors of the signal transducer and activator of transcription 3 (STAT3). It was determined that the anti-cancer and STAT3 inhibitory activity of the polymeric micellar cucurbitacins were comparable to the free drugs *in vitro* and *in vivo* in a B16-F10 melanoma cell line. Interestingly, the toxicity associated to cucurbitacin I and B was significantly reduced when these drugs were loaded into the nanoparticles[54].

A two-step nanoprecipitation method have been proposed for the synthesis of poly(caprolactone-*co*-lactide)-*b*-PEG-*b*-poly(caprolactone-*co*-lactide) block copolymer nanoparticles loaded with 10-hydroxycamptothecin (HCPT) (entrapment efficiency > 85 %). It was demonstrated that the HCPT-loaded nanoparticles developed a higher *in vitro* cytotoxicity, a superior *in vivo* anti-tumor activity and a remarkably different biodistribution in Sarcoma 180 (S180)-bearing mice than the free drug[55]. In addition, PCL-PEG-PCL nanoparticles were used as carriers for the water-insoluble drug oridonin in liver cancer treatment. This amphiphilic block copolymer (≈ 100 nm; entrapment efficiency ≈ 90 %) was

synthesized by an interfacial deposition method, in which the ring-opening polymerization of ε-CL was initiated by the –OH groups of PEG, with stannous octoate as catalyzer. The anti-tumor activity of the oridonin-loaded PCL-PEO-PCL nanoparticles was evaluated by measuring changes in tumor volume, tumor weight and survival rates of mice with grafted hepatoma (H22). The results indicated that this anti-tumor drug delivery system prolonged the survival time of mice and exhibited a higher therapeutic activity compared to free oridonin[56]. PCL-PEG-PCL nanoparticles were also used for the delivery of the biphenolic compound honokiol[28].

Poly(D,L-lactide-*ran*-ε-caprolactone)-poly(ethylene glycol)-poly(D,L-lactide-*ran*-ε-caprolactone) tri-block copolymers loaded with 5-FU (drug loading > 90 %) were prepared by ring-opening polymerization of D,L-lactide and ε-CL in the presence of PEG, using Zn L-lactate as initiator. The thermal behavior of the particles showed their potential as injectable drug-delivery devices: as the melting temperature approaches room temperature, a less porous inner structure is formed compared to the one under a higher melting temperature; this resulting in a slower drug release rate[57]. A novel self-assembled amphiphilic PCL grafted PVA copolymer (PCL-*g*-PVA) has been formulated by a dialysis method for the controlled release of PTX and DOX (up to 20 and 15 days, respectively)[29].

It has also been suggested the preparation of PCL nanoparticles surface-coated with chitosan for the delivery of Mitomycin C (MMC). The pharmacokinetic profile of the drug was improved by its vehiculization into the polymeric nanoparticles. Furthermore, this MMC-loaded nanoplatform showed a very efficient anti-tumor activity against a MB49 bladder carcinoma cell line[30].

Finally, PCL nanoparticles have also been used for gene delivery in cancer treatment. As an example, specific small interfering RNA (siRNAs) that target the estrogen receptor alpha (ERα) were encapsulated in PEGylated poly(ε-caprolactone-malic acid) (PEG-PCL/MA) nanocapsules (diameter: 100 – 200 nm, loading efficiency ≈ 70 %), as a novel strategy in the treatment of hormone-dependent breast cancers. Fluorescence quenching assays confirmed the incorporation of siRNA into the nanocapsule core. A persistent loss of ERα (90 % over 5 days) was observed in MCF-7 human breast cancer cells that were treated with this formulation. Furthermore, the intravenous injection of these nanocapsules into estradiol-stimulated MCF-7 cell xenografts led to a significant decrease in tumor growth and a decrease in ERα expression in tumor cells[58]. In this way, several studies have pointed out the benefits of the combination of nanotherapeutic strategies including both gene silencing and drug delivery, especially in the treatment of refractory tumors. As an example, PEO-PCL nanoparticles were formulated to efficiently encapsulate MDR-1 silencing siRNA and PTX. Upon administration in MDR $SKOV3_{TR}$ human ovarian adenocarcinoma cells, siRNA-mediated MDR-1 gene silencing was evident at a 100 nM dose. The combination of MDR-1 gene silencing and nanoparticle-mediated delivery significantly influenced the cytotoxic activity of PTX in $SKOV3_{TR}$ cells. The enhancement in cytotoxicity (action close to what was observed in drug sensitive SKOV3 cells) was attributed to an increase in the intracellular drug accumulation upon MDR-1 gene silencing, leading to an apoptotic cell-kill effect[59].

CONCLUSIONS

Poly(ε-caprolactone) colloids loaded with chemotherapy agents have shown in principle very promising results against cancer. However, in order to achieve an optimal anti-tumor activity, it is needed the control of the biological fate of these drug delivery systems. Therefore, significant engineering efforts should be focused on the development of poly(ε-caprolactone) nanocarriers able to respond to physiological or physical stimuli, as well as to enhance the delivery of drugs to targeted cancers. This involves the need for an effective drug transport into tumors, an adequate control of the biochemical factors regulating drug release and the maintenance of drug levels over the minimum cytotoxic concentration. Hence, the future of poly(ε-caprolactone) nanoplatforms in anticancer therapy will depend on advances in the design and nanoengineering of such kind of colloids, as well as on an improved understanding of tumor biology and biological barriers.

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