

# Development of implantable hydroxypropyl- $\beta$ -cyclodextrin coated polycaprolactone nanoparticles for the controlled delivery of docetaxel to solid tumors

Cem Varan · Erem Bilensoy

Received: 15 May 2014 / Accepted: 21 May 2014 / Published online: 6 June 2014  
© Springer Science+Business Media Dordrecht 2014

**Abstract** Treatment of cancer is one of the most challenging problems and conventional therapies are inadequate for targeted, effective and safe therapy. Development of nanoparticle-based drug delivery systems emerge as promising carriers in this field to ensure delivery of anti-cancer drug to tumor site. The aim of this study was to design hydroxypropyl- $\beta$ -cyclodextrin (CD) coated nanoparticles using poly( $\epsilon$ -caprolactone) (PCL) and its derivative poly(ethylene glycol)-block-poly( $\epsilon$ -caprolactone) (mePEG-PCL) to be applied as implants to tumor site following surgical operation in cancer patients. CD coated PCL and mePEG-PCL nanospheres were developed to encapsulate poorly soluble chemotherapeutic agent docetaxel (DOC) to improve solubility of drug and to enhance cellular penetration with longer residence time and higher local drug concentration. Nanospheres were prepared according to the nanoprecipitation method and coated with hydroxypropyl- $\beta$ -cyclodextrin (Cavasol<sup>®</sup> W7HP). Cyclodextrin coating was performed for higher drug encapsulation and controlled but complete drug release from nanoparticles. Nanoparticle diameters varied between 60 and 136 nm depending on polymer used for preparation and coating. All nanoparticles have negative surface charge and zeta potential values varied between  $-22$  and  $-37$  mV. Encapsulation efficiency of formulations were found to be between 46 and 73 % and CD coated

nanoparticles have significantly higher entrapment efficiency. Drug release profiles of nanoparticles were similar to each other and all formulations released encapsulated drug in approximately 12 h. Especially, CD-PCL nanoparticles were found to have highest entrapment efficiency and anticancer efficacy against MCF-7 human breast adenocarcinoma cell lines. Our study proved that polycaprolactone and its PEGylated derivatives can be suitable for development of implantable nanoparticles as a potential drug delivery system of DOC for cancer treatment and a good candidate for further in vivo studies.

**Keywords** Cyclodextrins · Docetaxel · Nanoparticle · Polycaprolactone · Polyethylene glycol · Tumor

## Introduction

Cancer is a major fatal disease globally with gradually increasing rate of incidence and it consists the cause of 25 % of all deaths [1]. Treatment of cancer is a challenging problem and conventional therapies are inadequate for effective and safe therapy. The most common problems for treatment of solid tumors is the insufficiency of chemotherapy following surgical operation and recurrence of cancer after therapy. The need for selective cytotoxicity against tumor cells left after removal of the solid tumor can be established by drug delivery to the tumor site with a lower therapeutic dose and by controlled release of the active ingredient at tumor tissues achieved by nanotechnology and nanoparticulate drug delivery systems. In fact, nanomedicines for cancer therapy have been approved by FDA and other health authorities in the last decade with new generations and follow-on products that are being developed [1–4].

C. Varan (✉) · E. Bilensoy  
Nanotechnology and Nanomedicine Division, Institute of  
Graduate Studies in Sciences, Hacettepe University, Beytepe,  
06800 Ankara, Turkey  
e-mail: varancem@gmail.com

E. Bilensoy  
Department of Pharmaceutical Technology, Faculty of  
Pharmacy, Hacettepe University, Sıhhiye, 06100 Ankara, Turkey

Docetaxel is a potent anticancer drug and inhibits microtubule polymerization in the cell. It is derived from the needles of the European Yew (*Taxus baccata*) and is accepted as a semi synthetic analogue of paclitaxel which is well-known anticancer drug. Both taxane drugs are used for treatment of cancer types such as breast, lung, ovarian, pancreatic, gastric, melanoma, soft tissue sarcoma, head and neck. In spite of their advantages, docetaxel and other taxane derivatives are very poorly soluble drugs in water so they are required to be formulated with solubilizers such as polysorbate 80 and cremophor EL for parenteral administration [5–8]. They have been reported to cause some side effects such as hypersensitivity reactions, neutropenia, nausea, vomiting, diarrhea, mucositis, erythema, desquamation, neuropathy, nail toxicity and fluid retention mostly due to the side effects caused by the solubilizers. To overcome these side effects and to improve water solubility, colloidal drug delivery systems such as polymeric nanoparticles, cyclodextrin complexes, liposomes, micelles and dendrimers are developed and these drugs are encapsulated in nanocarriers for safe and effective delivery [6, 9, 10].

Nanoparticle-based drug delivery systems are colloidal drug carrier systems with submicron particle size prepared mainly with synthetic or natural polymers. Most important advantage of nanoparticulate drug delivery systems over conventional drug delivery in cancer is that nanoparticles tend to accumulate in tumor tissue owing to their size via the Enhanced Permeation and Retention effect and release their load at the target site with therapeutic efficacy in a much lower dose. This also results in the reduction of dose-dependent side effects and leads to concentration dependent enhanced efficacy. Tumor targeting properties of nanoparticles can be enhanced by surface modification with antibodies, ligands or molecules that facilitate cellular uptake. Cationic polymers are used for this purpose increasing interaction with biological membranes and facilitating intracellular drug delivery surface modification can also alter drug encapsulation efficiency and drug release profile depending on the physicochemical properties of the active ingredient and its affinity to the core or shell polymer [11–16].

Poly( $\epsilon$ -caprolactone) (PCL) is hydrophobic, semi-crystalline polymer which is non-toxic, biodegradable and biocompatible. It is approved by FDA for therapeutic use and known to have a low degradation rate. Besides this, PCL-based systems have been used as suture material, wound dressing, contraceptive device, fixation device, scaffold material at tissue engineering and filling material at dentistry for several years [17–20]. PCL can be easily modified with other polymers and PCL derivatives can be obtained for varied purposes. It can copolymerize with hydrophilic polymers to form amphiphilic copolymers to

enhance its water solubility and prolong circulation time by repelling serum proteins. Poly(ethylene glycol)-block-poly( $\epsilon$ -caprolactone) (mePEG-PCL) copolymers, are obtained by copolymerization of PCL and PEG. This copolymer is more hydrophilic when compared with PCL. Besides, it is possible to prepare nanoparticles which can avoid the mononuclear phagocyte system (MPS) which is responsible for opsonization and clearance of foreign materials in the blood [21–26].

Cyclodextrins that are enzymatic degradation products of starch are also utilized to prepare or modify nanoparticles in the last decade. Cyclodextrins, cyclic oligosaccharides are known for modifying, the physicochemical properties of various drugs through formation of inclusion complexes. These non-covalent complexes offer a variety of physicochemical advantages such as increased water solubility and stability. Derivatives are reported to have mucosal penetration enhancer properties and improve solubility of drugs like docetaxel while reducing side effects. Hydroxypropyl- $\beta$ -cyclodextrin (HP- $\beta$ -CD) have been widely investigated for parenteral formulations because of its high solubility and non-toxicity. Cyclodextrin derivatives were in fact reported to improve stability of taxanes-based chemotherapy drugs against hydrolysis and increase cellular uptake [27]. Thus cyclodextrin coated nanoparticles is a good candidate for docetaxel loaded delivery system for high drug loading and good release properties.

In this study, PCL and its amphiphilic copolymer mePEG-PCL were used as core polymers to form nanoparticles able to encapsulate high amounts of hydrophobic drug docetaxel. These core nanoparticles were coated with a water soluble cyclodextrin HP- $\beta$ -CD for surface modification intended to allow controlled but complete release of the therapeutic load as well as to increase drug loading. The purpose of this study was to design docetaxel loaded and cyclodextrin coated nanoparticles using PCL and its derivative mePEG-PCL to be applied as implants to solid tumor site following surgical operation or injected at the tumor site in cancer patients. For this purpose, four different nanoparticle formulations were prepared and characteristic parameters such as particle size, polydispersity index (PDI), surface charge, drug loading capacity and drug release profiles were comparatively evaluated as well as anticancer efficacy in cell culture studies.

## Materials and methods

### Materials

Docetaxel (DOC) (MW: 807.88 g/mol, purity 97 %) was purchased from Fluka (Buchs, Switzerland). Poly- $\epsilon$ -caprolactone (PCL) (Mn: 80,000 Da) and Poly(ethylene

glycol)-block-poly( $\epsilon$ -caprolactone) methyl ether (mePEG-PCL) (PEG Mn:5,000 Da; PCL Mn: 5,000 Da) were purchased from Aldrich (St. Louis, MO, USA). Hydroxypropyl- $\beta$ -cyclodextrin (CAVASOL<sup>®</sup> W7 HP) (Mw: 1,400 Da) (CD) was supplied by Wacker Chemie AG (München, Germany). All organic solvent such as dichloromethane (DCM) (CHROMASOLV<sup>®</sup> Plus, for HPLC,  $\geq 99.9\%$ ), acetone (CHROMASOLV<sup>®</sup>, for HPLC,  $\geq 99.9\%$ ), acetonitrile (CHROMASOLV<sup>®</sup> Plus, for HPLC,  $\geq 99.9\%$ ) and surfactant Polysorbate 80 (TWEEN<sup>®</sup> 80) (MW: 1,310 Da) were supplied by Sigma Chemicals Co. (St. Louis, MO, USA). Ultrapure water was obtained from Millipore Simplicity 185 Ultrapure Water System (Millipore, France).

## Methods

### Preparation of nanospheres

Nanospheres were prepared according to the nanoprecipitation method introduced by Fessi et al. (1998) [28] modified for this study to give HP- $\beta$ -CD coated nanoparticles.

**Preparation of PCL and mePEG-PCL nanoparticles** Polymer (PCL or mePEG-PCL) was dissolved in acetone (% 0.1 w/v) under magnetic stirring and moderate heating. This organic solution consisting of polymers was added to ultrapure water (1:2 v/v). In this way, nanoparticles were spontaneously obtained. Organic solvent was evaporated under vacuum (IKA-Werke-RV06 ML, Germany) and removed to organic solvent waste. Nanoparticle aqueous dispersion was obtained in the desired final volume.

**Preparation of HP- $\beta$ -CD coated nanoparticles** Polymer (PCL or mePEG-PCL) was dissolved in acetone (% 0.1 w/v) under magnetic stirring and moderate heating. This organic solution consisting of polymers was added to water (1:2 v/v) which contains cyclodextrin (Cavasol<sup>®</sup> W7 HP) (% 0.01 w/v). In this way, nanoparticles were spontaneously obtained. Organic solvent was evaporated under vacuum (IKA-Werke-RV06 ML, Germany) and removed to organic solvent waste. Nanoparticle aqueous dispersion was obtained in the desired final volume.

Docetaxel was used as a model drug to prepare drug loaded nanoparticles. For preparation of drug loaded nanospheres, docetaxel (% 0.01 w/v) was dissolved in acetone with polymer before addition of organic solvent to ultrapure water.

All formulations were centrifuged at 3,500 rpm for 15 min (Hermle Z-323 K, Germany) and supernatant were separated to eliminate the polymer aggregates and free drug.

### *In vitro* characterization of nanospheres

**Particle size distribution** Mean particle size (nm) and polydispersity index (PDI) values of all formulations were determined by Malvern NanoZS (Malvern Instruments, UK) which use quasi-elastic light scattering technique (QELS). All formulations were measured in disposable capillary cell and determined at an angle of 173° and room temperature (n = 3).

**Surface charge** Surface charge (mV) of all formulations were determined by Malvern NanoZS (Malvern Instruments, UK) and calculated as zeta potential. All formulations were determined at room temperature (n = 3).

**Encapsulation efficiency** Encapsulated drug quantity of drug loaded formulations were determined directly using an analytically validated HPLC method (HP Agilent 1100 HPLC system, Germany). Drug loaded nanoparticles have been lyophilized for 24 h and obtained in powder form. This powder was dissolved in DCM to expose encapsulated drug and added to acetonitrile (1:10 v/v). DCM were evaporated under nitrogen and suspension were analyzed by analytically validated HPLC technique ( $r^2 = 0.9999$ ). Chromatographic separation was achieved using an ODS column at 25° C (Develosil ODS-UG-5 4.6 mm/150 mm 5.6  $\mu$ m). Mixture of ultrawater/acetonitrile (50:50) was used as mobile phase. The flow rate was set to 1.0 mL/min, UV detection wavelength was 229.6 nm and the retention time of DOC was about 8.4 min. Associated Drug (%), Entrapment Efficiency (see Eq. 2), Entrapped Drug Quantity (see Eq. 3) were calculated as follows;

$$\text{Associated drug (\%)} = \frac{\text{determined DOC quantity } (\mu\text{g})}{\text{initial DOC quantity } (\mu\text{g})} \times 100 \quad (1)$$

$$\text{Entrapment Efficiency (\%)} = \frac{\text{DOC quantity } (\mu\text{g})}{\text{Polymer quantity (mg)}} \times 100 \quad (2)$$

$$\text{Entrapped Drug Quantity} = \frac{\text{DOC quantity } (\mu\text{g})}{\text{Formulation volume (mL)}} \quad (3)$$

**Drug release** Release profile of drug loaded formulations were determined using dialysis technique in PBS buffer (pH 7.4) containing 0.1 % Tween 80 providing sink conditions. Nanoparticle suspensions were put in dialysis membrane bag (Cellulose Membrane MWCO: 100,000 Da, Sigma Chemicals Co., USA) placed release medium in PBS buffer and held in a thermostated shaker bath system

(Memmert, Schwabach, Germany) at 37 °C. At predetermined time intervals (1, 2, 4, 6, 12 h), 0.5 mL samples were withdrawn from the system replaced with same volume of fresh medium and DOC content was determined with HPLC technique to obtain cumulative drug release profile.

### Anticancer efficacy

Anticancer efficacy of docetaxel encapsulated into CD-coated nanoparticles were evaluated in terms of cell viability based upon MTT assay. In this context, docetaxel solution was compared to equivalent concentration of docetaxel loaded into PCL, mePEG-PCL, CD-PCL and CD-mePEG-PCL nanoparticles.

MCF-7 human breast adenocarcinoma cell line were obtained from the American Type Culture Collection (ATCC, LGC Promochem, Rockville, MD, USA) and all reagents were obtained from Biochrom (Berlin, Germany). Cell line was cultured in Dulbecco's MEM, supplemented with 10 % fetal bovine serum (FBS), penicillin (100 units/mL) and streptomycin (100 µg/mL). The cultures were maintained at 37 °C in a humidified 5 % CO<sub>2</sub> incubator.

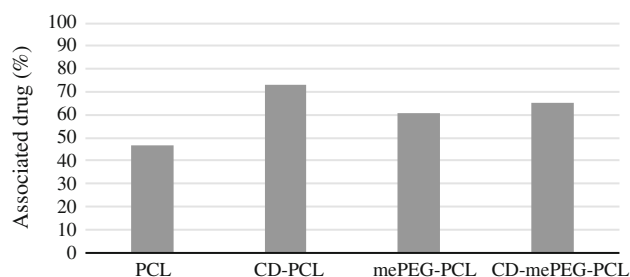
The anticancer efficacy of DOC-loaded nanospheres formulations PCL, CD-PCL, mePEG-PCL and CD-mePEG-PCL were determined against MCF-7 cell line with MTT assay. DOC solution used in the cytotoxicity assays was prepared in dimethyl sulfoxide. DOC concentrations in the formulations and solution were maintained in the same range throughout the cytotoxicity studies. MCF-7 cells were resuspended in complete medium and seeded in 96-well tissue culture plates at a concentration of  $10 \times 10^3/100 \mu\text{L}$  per well. The cells were allowed to attach to the surface for 24 h and then exposed to 100 µL of diluted formulations which contain 1 µM DOC in DMEM. After 72 h of incubation, 25 µL of MTT solution (5 mg/mL) were added. The formazan crystals produced were solubilized by adding 200 µL DMSO. Optical densities (OD) were read at 450 nm using a microplate reader (Molecular Devices, USA). The cells incubated in culture medium alone served as a control for cell viability. All assays were performed in quadruplicate and mean OD values were used to estimate the cell viability.

## Results

Particle size, polydispersity index and zeta potential values of nanoparticles are presented in Table 1. Particle size of nanoparticle formulations were found to be optimum between the range of 60 and 136 nm suitable for longer circulation and facilitates cellular uptake. Polydispersity

**Table 1** Mean diameter, zeta potential and polydispersity index of nanoparticle formulations

	Mean diameter (nm)	Polydispersity index	Zeta potential (mV)
PCL	126.8 ±0.1528	0.078 ±0.007	-37.2 ±0.551
CD-PCL	136.0 ±1.473	0.090 ±0.021	-34.8 ±0.529
mePEG-PCL	60.85 ±0.9804	0.160 ±0.010	-22.1 ±4.55
CD-mePEG-PCL	74.44 ±0.7753	0.328 ±0.010	-25.6 ±1.50



**Fig. 1** Effect of CD coating on docetaxel loading efficiency

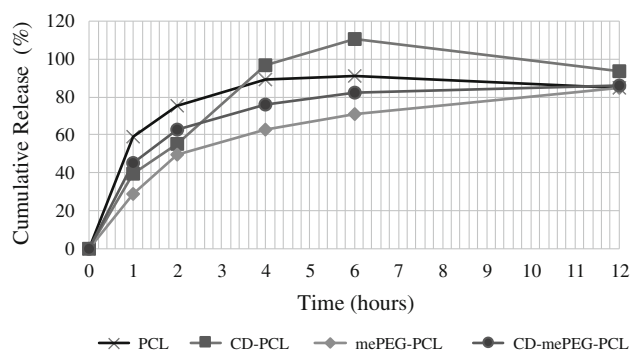
**Table 2** Associated drug (%), entrapment efficiency (%) and entrapped drug quantity of formulations

	Associated drug (%)	Entrapment efficiency (%)	Entrapped drug quantity
PCL	46.48	9.39	51.64
CD-PCL	73.26	15.11	81.4
mePEG-PCL	60.97	12.19	67.74
CD-mePEG-PCL	65.06	13.01	72.28

index of all formulations were found to be below 0.33 and indicate unidisperse homogeneous nanoparticles. Zeta potential values are between -22 to -37 mV. Coating with cyclodextrin caused to increase of particle size about 9–13 nm.

Associated drug (%) of formulations were found to be between 46 and 73 % and effects of CD coating on drug loading can easily be observed in Fig. 1. Associated drug (%), Entrapment Efficiency (%) and Entrapped Drug Quantity of formulations are presented in Table 2. mePEG-PCL nanoparticles have higher entrapment efficiency when compared to PCL nanoparticles. The highest entrapment efficiency was found with CD-PCL (15 %).

As a result of in vitro release studies, it was observed that all formulations release encapsulated drug in about 12 h as seen in Fig. 2.



**Fig. 2** In vitro docetaxel release profile from nanoparticles

Anticancer efficacy of DOC-loaded nanospheres were evaluated on MCF-7 cells and all formulations have significant cytotoxic effect on MCF-7 cells as shown in Fig. 3. Especially, DOC-loaded CD-PCL nanospheres have higher cytotoxicity when compared to other formulations and DOC solution.

CD coating was found to exert its effect on mean diameter as an increase of approximately 10 nm followed by a significant increase in drug loading. CD coating also accelerated the release of docetaxel from the nanoparticles.

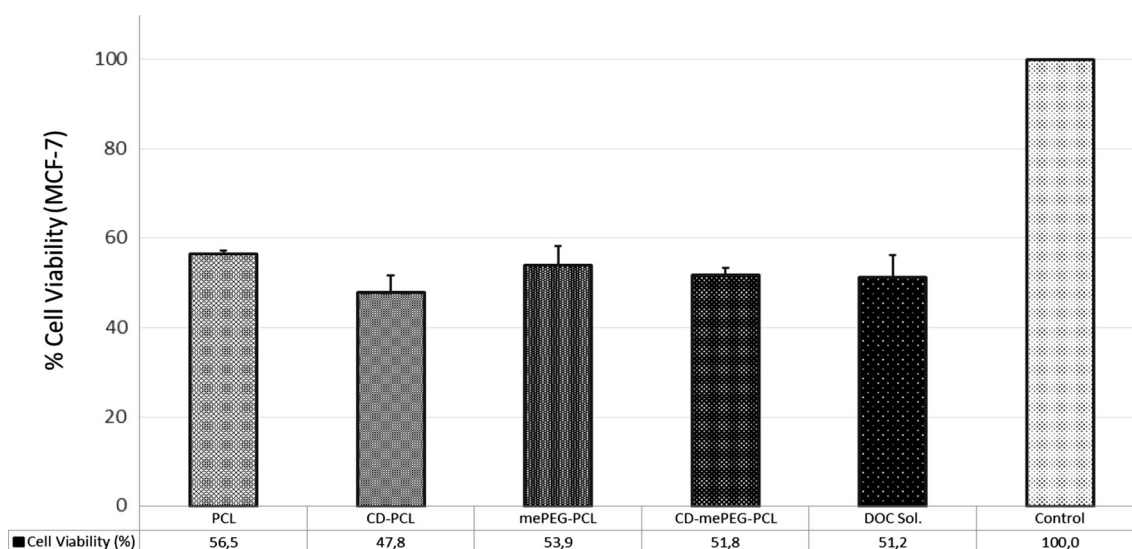
## Discussion

Particle size of drug carrier systems which are above 400 nm are important for cellular uptake. Studies showed that nanoparticles which have smaller particle size can enter the cancer cell more easily and quickly [29, 30].

Polydispersity index of all formulations were found to be below 0.33 and acceptable indicating homogeneous size distribution. Zeta potential values are between  $-22$  to  $-37$  mV. It was reported that nanoparticles which have between  $-30$  mV and  $+30$  mV zeta potential value are more stable and increase of these values at negative or positive direction causes aggregation risk [31, 32]. Even though, zeta potential values of PCL ( $-37.2$  mV) and CD-PCL ( $-34.8$  mV) were slightly higher than  $-30$  mV, no aggregation have been observed during experimental study.

Coating with cyclodextrin caused increase of particle size, indicating presence of cyclodextrin coating layer on surface of nanoparticles. Zeta potential values also confirmed these results. CD has neutral zeta potential and it was supposed that coating with CD reduce surface charge [33]. In fact, cyclodextrins were reported to have very low effect on zeta potential of nanoparticles of iron [34]. Our results showed that surface charge of PCL nanoparticles were reduced about 3 mV after coating with CD. Nanoparticles which prepared from mePEG-PCL have smaller particle size than PCL nanoparticles. mePEG-PCL copolymers are more soluble in water compared to PCL because of amphiphilic properties of mePEG-PCL. This properties can be effective on smaller particle size and mePEG-PCL nanoparticles were reported to have smaller particle size compared to PCL nanoparticles [35].

When Table 2 is examined for the loading properties of docetaxel to PCL and mePEG-PCL nanoparticles and effect of CD coating on encapsulation efficiency, it is clearly seen that CD coating results in a twofold increase in drug loading for PCL nanoparticles. This can be attributed to the fact that hydrophobic docetaxel will have a high affinity to the apolar



**Fig. 3** Cell viability (%) of MCF-7 human breast adenocarcinoma cells treated with docetaxel solution and docetaxel in nanoparticles ( $\pm$ SD,  $n = 3$ )

cavity of HP- $\beta$ -CD in the coating layer of the nanoparticles. This affinity was demonstrated previously in several studies [36–39]. It is also noteworthy that this effect is much less pronounced for mePEG-PCL nanoparticles. mePEG-PCL nanoparticles already have amphiphilic properties due to hydrophilic PEG chains and hydrophobic PCL in the same structure. Although resulting nanoparticles are smaller in size thanks to this amphiphilicity. PEG chains may cause steric hindrance and prevent the hydrophobic drug to be encapsulated with in the nanoparticle matrix.

Figure 2 representing the release behaviour of DOC from different nanoparticles suggest a controlled release profile for all nanoparticles. mePEG-PCL and CD-mePEG-PCL released the drug somewhat smaller. Nevertheless all formulations released about 50 % of drug load in the first 1 h followed by a controlled liberation of complete load in 12 h. Fastest release profile was obtained with CD-PCL nanoparticles with complete release within 4 h. It can be suggested that solubilization properties of HP- $\beta$ -CD helped facilitate and accelerate drug release from PCL nanoparticles. The fact that a burst effect is observed within the first hour may indicate that a significant percentage of the drug is adsorbed or included in the nanoparticle surface.

Figure 3 represent the anticancer efficacy of docetaxel in DMSO in comparison to docetaxel incorporated in nanoparticles. It is clearly seen that all nanoparticle formulations were proved to exert equivalent anticancer effect as drug solution in DMSO. Docetaxel in CD-PCL nanoparticles were demonstrated to be slightly more effective than other formulations probably due to the high drug loading and fast release behavior.

## Conclusion

In the light of the data obtained in this study, it can be concluded that formulations which were prepared with mePEG-PCL as polymer have significantly smaller particle size and longer drug release profile compared to other PCL formulations. Even though coating with cyclodextrin significantly increased encapsulation efficiency and anticancer activity, particle size and polydispersity index remained unchanged. HP- $\beta$ -CD coated PCL nanoparticles can be considered as promising systems for docetaxel delivery for injectable or implantable nanoparticles with favorable size and loading for eventual intracellular drug delivery.

## References

1. Pathak, P., Kathiyar, V.K.: Multi-functional nanoparticles and their role in cancer drug delivery—a review. *Azonano*. **3**, 1–17 (2007)
2. Luo, Y., Prestwich, G.D.: Cancer-targeted polymeric drugs. *Curr. Cancer Drug Targets* **2**(3), 209–226 (2002)
3. Bharali, D.J., Khalil, M., Gurbuz, M.: Nanoparticles and cancer therapy: a concise review with emphasis on dendrimers. *Int. J. Nanomed.* **4**, 1–7 (2009)
4. Kim, K.Y.: Nanotechnology platforms and physiological challenges for cancer therapeutics. *Nanomed. Nanotechnol. Biol. Med.* **3**(2), 103–110 (2007)
5. Guenard, D., Voegeléin-Gueritte, F., Potier, P.: Taxol and Taxotere: discovery, chemistry, and structure-activity relationships. *Acc. Chem. Res.* **26**, 160–167 (1993)
6. Verweij, J., Clavel, M., Chevalier, B.: Paclitaxel (Taxol<sup>TM</sup>) and docetaxel (Taxotere<sup>TM</sup>): not simply two of a kind. *Ann. Oncol.* **5**, 495–505 (1994)
7. Sampath, P., Rhines, L.D., DiMeco, F., Tyler, B.M., Park, M.C., Brem, H.: Interstitial docetaxel (Taxotere): novel treatment for experimental malignant glioma. *J. Neurooncol.* **80**(1), 9–17 (2006)
8. Moes, J., Koolen, S., Huitema, A., Schellens, J., Beijnen, J., Nuijen, B.: Development of an oral solid dispersion formulation for use in low-dose metronomic chemotherapy of paclitaxel. *Eur. J. Pharm. Biopharm.* **83**(1), 87–94 (2013)
9. Immordino, M.L., Brusa, P., Arpicco, S., Stella, B., Dosio, F., Cattel, L.: Preparation, characterization, cytotoxicity and pharmacokinetics of liposomes containing docetaxel. *J. Controll. Release* **91**(3), 417–429 (2003)
10. Baker, J., Ajani, J., Scotte, F., Winther, D., Martin, M., Aapro, M.S., Minckwitz, G.: Docetaxel-related side effects and their management. *Eur. J. Oncol. Nurs.* **13**, 49–59 (2009)
11. Mora-Huertas, C., Fessi, H., Elaissari, A.: Polymer-based nanocapsules for drug delivery. *Int. J. Pharm.* **385**, 113–142 (2010)
12. Zelphati, O., Uyechi, L., Barron, L., Szoka, F.: *Biochimica et Biophysica Acta (BBA)—Lipids and Lipid. Metabolism* **1390**, 119–133 (1998)
13. Quintanar-Guerrero, D., Allémann, E., Fessi, H., Doelker, E.: Drug development and industrial pharmacy. *Drug Dev. Ind. Pharm.* **24**, 1113–1128 (1998)
14. Parveen, S., Misra, R., Sahoo, S.: Nanoparticles: a boon to drug delivery, therapeutics, diagnostics and imaging. *Nanomed. Nanotechnol. Biol. Med.* **8**(2), 147–166 (2012)
15. Lundqvist, M., Stigler, J., Elia, G., Lynch, I.: Nanoparticle size and surface properties determine the protein corona with possible implications for biological impacts. *PNAS* **15**, 14265–14270 (2008)
16. Bilensoy, E.: Cationic nanoparticles for cancer therapy. *Expert Opin. Drug Deliv.* **7**, 795–809 (2010)
17. Woodruff, M.A., Huttmacher, D.W.: The return of a forgotten polymer-polycaprolactone in the 21st century. *Prog. Polym. Sci.* **35**, 1217–1256 (2010)
18. Sinha, V.R., Bansal, K., Kaushik, R., Kumria, R., Trehan, A.: Poly-epsilon-caprolactone microspheres and nanospheres: an overview. *Int. J. Pharm.* **278**(1), 1–23 (2004)
19. Gad, S.C.: *Pharmaceutical Manufacturing Handbook: Production and Processes*, 544–545. Wiley-Interscience, New Jersey (2008), ISBN 978-0-470-25958-0
20. Schubert, S., Delaney, J.T., Schubert, U.S.: Nanoprecipitation and nanoformulation of polymers: from history to powerful possibilities beyond poly(lactic acid). *R. Soc. Chem. Soft Matter* **7**, 1581–1588 (2011)
21. Gref, R., Lück, M., Quellec, P., Marchand, M., Dellacherie, E., Harnisch, S.: ‘Stealth’ corona-core nanoparticles surface modified by polyethylene glycol (PEG): influences of the corona (PEG chain length and surface density) and of the core composition on phagocytic uptake and plasma protein adsorption. *Colloids Surf. B* **18**, 301–313 (2000)

22. Choi, C., Chae, S.Y., Kim, T.-H., Jang, M.-K., Cho, C.S., Nah, J.-W.: Preparation and characterizations of poly(ethylene glycol)-poly( $\epsilon$ -caprolactone) block copolymer nanoparticles. *Bull. Korean Chem. Soc.* **26**(4), 523–528 (2005)
23. Zhou, S., Deng, X., Yang, H.: Biodegradable poly( $\epsilon$ -caprolactone)-poly(ethylene glycol) block copolymers: characterization and their use as drug carriers for a controlled delivery system. *Biomaterials* **24**, 3563–3570 (2003)
24. Liu, Q., Li, R., Zhu, Z., Qian, X., Guan, W., Yu, L.: Enhanced antitumor efficacy, biodistribution and penetration of docetaxel-loaded biodegradable nanoparticles. *Int. J. Pharm.* **430**(1–2), 350–358 (2012)
25. Wei, X.W., Gong, C.Y., Gou, M.Y., Fu, S.Z., Guo, Q.F., Shi, S.: Biodegradable poly(epsilon-caprolactone)-poly(ethylene glycol) copolymers as drug delivery system. *Int. J. Pharm.* **381**(1), 1–18 (2009)
26. Li, R., Li, X., Xie, L., Ding, D., Hu, Y., Qian, X.: Preparation and evaluation of PEG–PCL nanoparticles for local tetradrine delivery. *Int. J. Pharm.* **379**, 158–166 (2009)
27. Challa, R., Ahuja, A., Ali, J., Khar, R.K.: Cyclodextrins in drug delivery: an updated review. *AAPS PharmSciTech* **6**(2), E329–E357 (2005)
28. Fessi, H., Devissaguet, J.P., Thies, C.: Process for the preparation of dispersible colloidal systems of a substance in the form of nanospheres. US Patent 5,118,528 (1998)
29. Brigger, I., Dubernet, C., Couvreur, P.: Nanoparticles in cancer therapy and diagnosis. *Adv. Drug Deliv. Rev.* **54**, 631–651 (2002)
30. Win, K.Y., Feng, S.S.: Effects of particle size and surface coating on cellular uptake of polymeric nanoparticles for oral delivery of anticancer drugs. *Biomaterials* **26**(15), 2713–2722 (2005)
31. Muller, R.H., Jacobs, C., Kayser, O.: Nanosuspensions as particulate drug formulations in therapy. Rationale for development and what we can expect for the future. *Adv. Drug Deliv. Rev.* **47**(1), 3–19 (2001)
32. Hans, M.L., Lowman, A.M.: Biodegradable nanoparticles for drug delivery and targeting. *Curr. Opin. Solid State Mater. Sci.* **6**(4), 319–327 (2002)
33. Boudad, H., Legrand, P., Lebas, G., Cheron, M., Duchêne, D., Ponchel, G.: Combined hydroxypropyl- $\beta$ -cyclodextrin and poly(alkylcyanoacrylate) nanoparticles intended for oral administration of saquinavir. *Int. J. Pharm.* **218**(1–2), 113–124 (2001)
34. Cameselle, C., Reddy, K.R., Darko-Kagya, K., Khodadoust, A.: Effect of dispersant on transport of nanoscale iron particles in soils: zeta potential measurements and column experiments. *J. Environ. Eng.* **139**(1), 23–33 (2013)
35. Xin, H., Chen, L., Gu, J., Ren, X., Wei, Z., Luo, J., Chen, Y., Jiang, X., Sha, X., Fang, X.: Enhanced anti-glioblastoma efficacy by PTX-loaded PEGylated poly( $\epsilon$ -caprolactone) nanoparticles: in vitro and in vivo evaluation. *Int. J. Pharm.* **402**, 238–247 (2010)
36. Bilensoy, E., Hincal, A.A.: Recent advances and future directions in amphiphilic cyclodextrin nanoparticles. *Expert Opin. Drug Deliv.* **6**(11), 1161–1173 (2009)
37. Thiele, C., Auerbach, D., Jung, G., Wenz, G.: Inclusion of chemotherapeutic agents in substituted  $\beta$ -cyclodextrin derivatives. *J. Incl. Phenom. Macrocycl. Chem.* **69**, 303–307 (2011)
38. Park, M.H., Keum, C.G., Song, J.Y., Kim, D., Cho, C.W.: A novel aqueous parenteral formulation of docetaxel using prodrugs. *Int. J. Pharm.* **462**, 1–7 (2014)
39. Agüeros, M., Zabaleta, V., Espuelas, S., Campanero, M.A., Irache, J.M.: Increased oral bioavailability of paclitaxel by its encapsulation through complex formation with cyclodextrins in poly(anhydride) nanoparticles. *J. Controll. Release* **145**, 2–8 (2010)