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Research Article

Biodegradable Electrospun Polyester-Urethane Nanofiber Scaffold: Codelivery Investigation of Doxorubicin-Ezetimibe and Its Synergistic Effect on Prostate Cancer Cell Line

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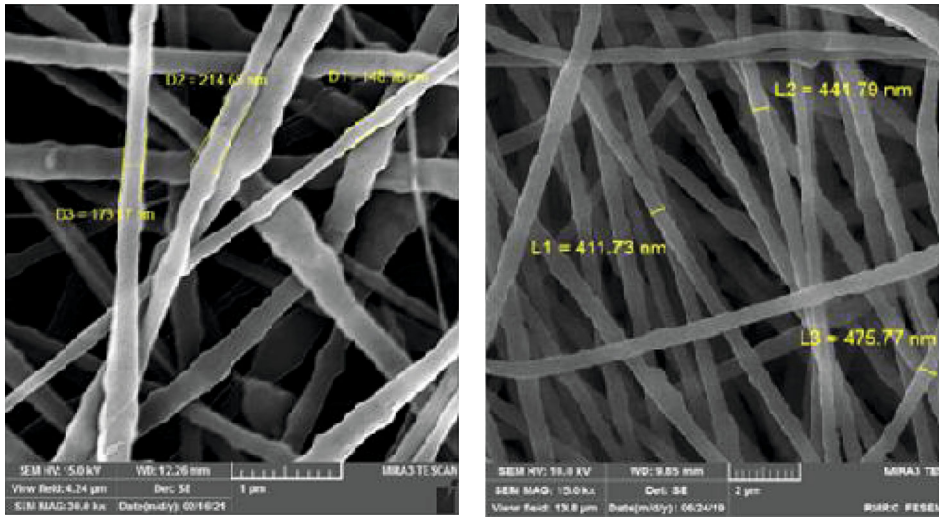
Electrospun nanofiber-mediated drug-delivery systems are extensively applied for the controlled delivery of anticancer agents and localized cancer chemotherapy. In this work, we assessed the synergistic anticancer effect of polyurethane-polycaprolactone (PU-PCL) nanofibers (NFs) on prostate cancer cell line (PC3) and evaluate their antitumor activity in vitro. Polyurethane-polycaprolactone (PU-PCL) nanofibers were prepared by electrospinning and used for codelivery of doxorubicin hydrochloride (DOX) and ezetimibe (EZ). The morphology, weight loss, and swelling ability of the PU-PCL nanofibers were characterized. Drug release test was performed by UV-vis spectroscopy in a phosphate buffer at pH 7.4 at 37°C. The viability of the PC3 prostate cancer cells was evaluated by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay for the different periods of cell incubation. PC3 prostate cancer cells were treated with different concentrations of 0-50 μg/ml of DOX, EZ, DOX-loaded NFs, EZ-loaded NFs, and DOX-EZ coloaded NFs for 48 hours. The results demonstrated that electrospun PU-PCL NFs showed significant synergistic therapeutic efficacy on prostate cancer cells. This study proposes that the DOX-EZ codelivery using PU-PCL nanofibrous scaffold could be used as a possible approach for anticancer drug delivery for the treatment of prostate cancer.

1. Introduction

Prostate cancer, as a worldwide health concern, is one of the most important commonly seen in males [1, 2]. Most prostate cancers grow slowly without any health risks to the patients. Nonetheless, cancer cells can proliferate rapidly, resulting in tumor growth and spreading to other areas of the body [1]. Currently, chemotherapy surgery and radiation therapy are major therapeutic approaches for the treatment of prostate cancer [2]. Despite many advancements, adverse effects such as hair loss, nausea, weight loss, heart poisoning, and the emergence of resistance to existing anticancer medications need an urgent and necessary search for new anticancer agents. In this way, nanomedicine and combination chemotherapy, which incorporates two or more different medications for use simultaneously, have gained a reputation due to their advantages, such as reducing the dose of the drug and achieving more therapeutic efficacy [3, 4].

Doxorubicin (DOX), an anticancer drug, is frequently used to treat malignant cancerous tumors alone and combined with other cancer drugs to treat a variety of cancers, including prostate cancer. Although the clinical application of DOX is affected because of its high toxicity, the release control of the drug into tumor cells, at the right time and place, results in



(a) (b)

Figure 1: (a) Scanning electron microscopy image of PCL-Diol-b-PU nanofibers. (b) Scanning electron microscopy image of DOX/EZ-loaded PU-PCL nanofibers.

reduced drug toxicity and side effects [5, 6]. Also, ezetimibe as an angiogenesis inhibitor has been used in the treatment of prostate cancer tumors [7].

There is ample evidence that biodegradable polymers and antioxidants have been used widely in medicine due to their fewer side effect in healthy cells [8, 9]. In other words, the general concept of biocompatibility is based on the interaction of a substance with its biological environment. In many cases, the reaction of tissues and cells is characterized by an inflammatory response. Anticancer medicines are frequently delivered locally using polymer nanoparticles [10–16]. Numerous drug delivery technologies, such as polymer nanoparticles [8, 9, 15–17], have been used to load anticancer medications to improve the targeting of tumors and reduce hazardous adverse health problems of chemotherapeutic treatments [17–21]. Numerous drug delivery technologies, such as polymer nanoparticles, have been used to load anticancer medications in order [21, 22]. Polyester-urethane is synthesis in numerous forms such as nanoparticles, micelles, scaffolds, nanogels, nanofibers, and complexes with DNA using different methods and modification options for medical applications including cardiovascular diseases, cancer, and tissue engineering [22, 23].

Nanofibers as one of the nanostructures in drug delivery are prepared by the electrospinning method using biodegradable polymers [10, 11, 22, 23]. For instance, to prepare drug-carrying nanofibers, mesoporous DOX silica nanoparticles were incorporated successfully into nanoplasma fibers as nanoimplantable local scaffolds for the treatment of potential cancer [5, 11, 24]. Various drugs such as dichloroacetate, paclitaxel, and doxorubicin have been loaded into nanofibers [25–28].

Recent *in vivo* studies have shown that biodegradable polyurethane foams are biocompatible without any toxic or carcinogenic effects on the body, even though these polyurethanes activate macrophages [25–28]. Because of their high stability, mechanical flexibility, and biocompatibility, polyurethanes have been widely used in the manufacturing of medical devices for over 40 years. Polyurethanes can be manufactured in a variety of forms, including foam products, films, elastomers, powders, liquids, nanofibers, and emulsions [29]. PCL-Diol-b-PU/gold nanofiber-electrospinning has been developed for continuous drug delivery of temozolomide (TMZ) [30] for scroll treatment [31]. Also, polyurethane nanofibers have been used as nanoimplantable scaffolds for DOX delivery in cancer treatment [11, 32].

In the current study, the PU-PCL nanofibrous implants were applied for constant delivery of DOX and Ez simultaneously against prostate cancer.

2. Methods and Materials

2.1. Materials and Instruments. IR spectra (KBr discs) were verified with (Equinox 55 LS 101 Bruker, German). ^{1}HNMR and ^{13}CNMR spectra have been recorded in DMSO-d6 (5% and 20% (*w*/*v*)) using a Bruker Avance III-400 MHz (Bruker Bioscience, MA, USA). Without additional purification, all commercially accessible chemicals and reagents were employed. Tetrahydrofuran (THF) and 4 butanediols (propylene glycol) polycaprolactone (PU-PCL) were obtained from Merck (Merck, Germany). Doxorubicin hydrochloride, phosphate buffer saline (pH of 7.4, PBS), and ezetimibe were purchased from Merck, and Sigma-Aldrich (Aldrich, USA).

2.2. Preparation and Characterization. PU-PCL nanofibers were prepared using the previously described method. SEM was used to examine the morphology of PU-PCL nanofibers and DOX/EZ/PU-PCL nanofibers. FTIR and NMR spectra were recorded by FTIR spectrometer (Equinox 55 LS 101 Bruker, German) and Bruker Avance III-400 MHz (MA, USA), respectively. In brief, the drugs were characterized using infrared spectroscopy (FTIR), the Fourier transform, the polymer structure, and promising interactions between

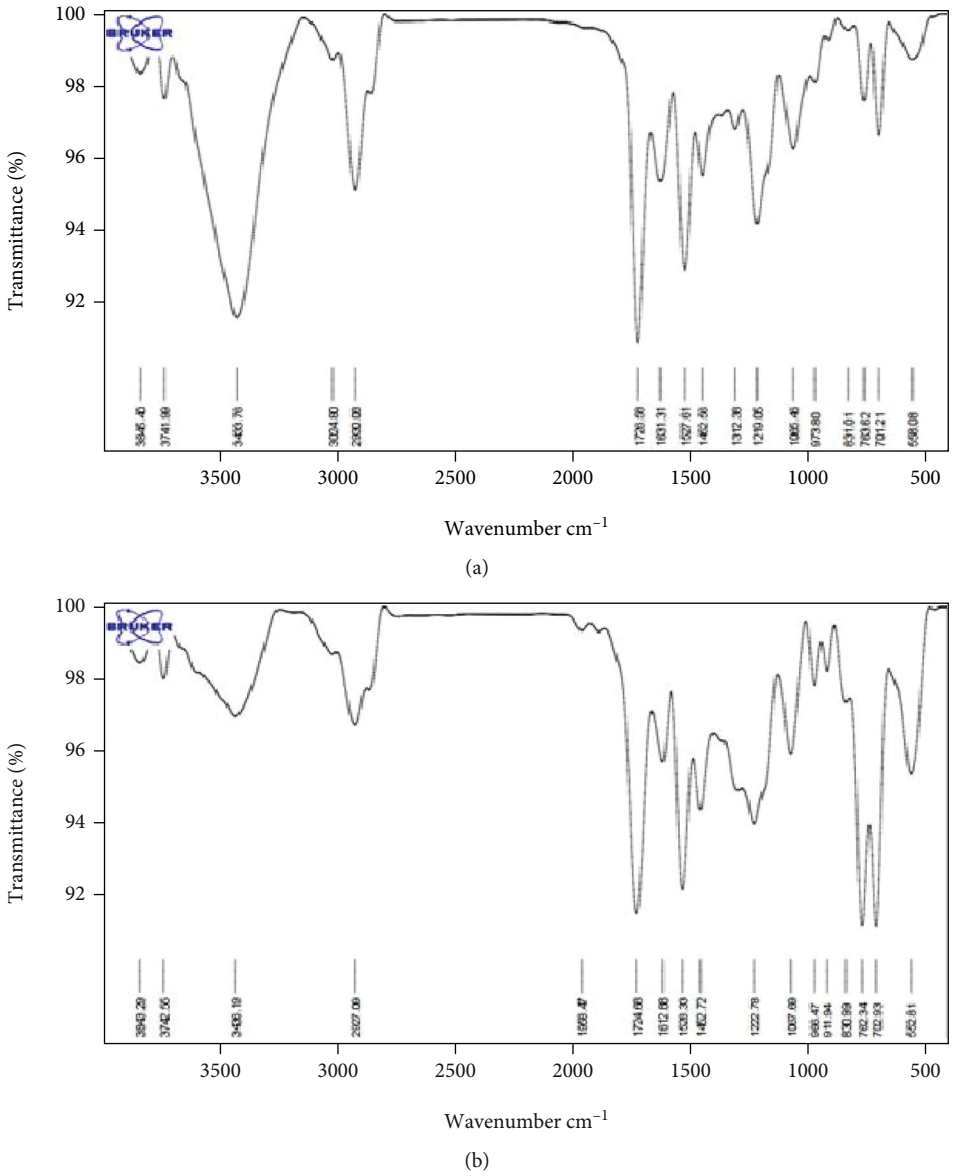


Figure 2: (a) FTIR spectra of PU-PCL nanofibers. (b) FTIR spectra of DOX/EZ loaded PU-PCL nanofibers.

the polymers. The samples' infrared spectra (IR) were scanned in 400-4000 cm^{-1}. NMR spectrometer (400.1 MHz) was used for 1 h to gather 1HNMR spectra, with DMSO-d6 as a solvent in 5% (*w*/*v*) concentration 1HNMR and roughly 20% (*w*/*v*) for 13CNMR. At room temperature, all spectra have been recorded (298 K).

2.3. General Procedure for Preparation of DOX/EZ/PU-PCL Nanofibers Using Electrospinning. For the preparation of PU-PCL nanofibers, first, 400 mg of PU-PCL polymer was dissolved in DMF/THF (1/2 *v*/*v*) solvent while stirring at 30°C for 24 h. After that, the solution was placed in a plastic syringe with a syringe needle (19 gauge nozzles). The PU-PCL nanofibers are produced by applying a voltage above 25.5 kV. The feeding rate of the speed collector and solution in the electrospinning procedure was 2 mL h^{-1}.

2.4. Drug Loading Efficiency. The drug loading efficacy was determined as follows. Initially, DOX, EZ, and DOX/EZ were added to the prepared nanofibers, and the mix was stirred in DMF/THF at room temperature for 4 h. The solution's absorbance was measured using UV-vis at 266 nm to determine the drug loading. The below formula was used to calculate the efficiency of drug loading (DLE%):

$$\text{DLE\%} = \frac{\text{Actual drug content}}{\text{Initial drug}} \times 100\%. \quad (1)$$

2.5. Drug Release Study. The drug release expressed at different pH conditions was assessed. Briefly, the 2 mg of prepared nanofibers containing DOX/EZ was incubated at 37°C in phosphate-buffered saline (pH 7.4, PBS, 0.05 M) and acetate buffer solution (pH 5.4) in a shaker at 37°C and 40°C (Grant

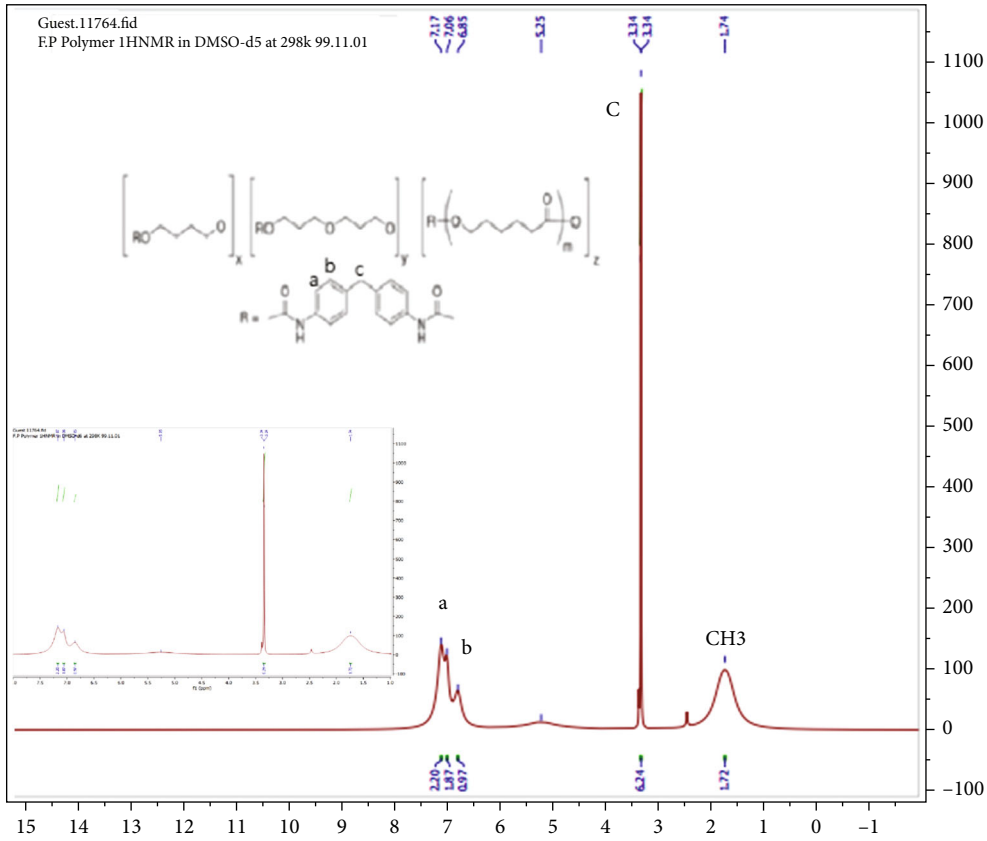


Figure 3: The ^{1}HNMR spectrum of the PU-PCL polymers.

Table 1: The drug loading efficiency of nanofibrous formulations nanofibers.

Formulation	Drugs	Drugs content (drug/polymer)	Drug loading efficiency
DOX/PU-PCL	DOX	14/100	98%
EZ/PU-PCL	EZ	10/100	95%
DOX/EZ/PU-PCL	DOX	7/100	95%
DOX/EZ/PU-PCL	EZ	5/100	97%

tools, Cambridge, England) for 10 days. At periods (0.5, 1, 2, 4, 5, 24, 48, 72, 96, and 168 h), the quantity of released DOX, EZ, and DOX/EZ was determined by taking 2 ml of the solution released from the dissolution medium. After that, an equal amount of fresh medium of PBS solution was added to the incubation media. Released drugs were measured using the EZ and DOX calibration curves in a similar buffer, and comparative percentage was considered as a role of incubation time in terms of the quantity of the anticancer agent existing in the scaffold [5].

2.6. Cell Culture. The ATCC suggested that the prostate cancer cell line PC3 ((PC-3) is a human prostate cancer cell line) was supported by the Pasteur Institute (Iran) and cultivated as directed. The cells were cultured at 37°C with 5% CO_2 in RPMI-1640 with penicillin (100 U/mL), 10% FBS, streptomycin (100 U/mL), and L-glutamine (300 g/mL).

2.7. Cell Toxicity Assay. A drug release test was performed in a cell culture medium for 24 and 48 h. We do not have an opinion about pH: 2 to evaluate drug release, because our goal is an assessment of the drug in the Kansari cell environment and that environment is pH: 5.4, and pH: 2 is not a Kansari environment. The in vitro MTT test was used to examine the cytotoxic effects of the produced compounds [33–35]. The PC-3 cells with 12,000 per well were seeded on 96-well plates at a density of and incubated at 37°C and 5% CO_2 for 24/48 h. Then, DOX, EZ, DOX/EZ, DOX/PU-PCL (20 mg) nanofibers, EZ/PU-PCL (20 mg) nanofibers, and DOX/EZ/PU-PCL (20 mg) for different times (1% DMSO) were added to cell media. The negative control was a comprehensive medium comprising 1% DMSO. The wells were then filled with MTT solution at a final concentration of 0.5 mg/mL. After 4 hours, the solution was precisely aspirated from the wells, and 100 L DMSO was added to each well to dissolve the formazan crystals. To

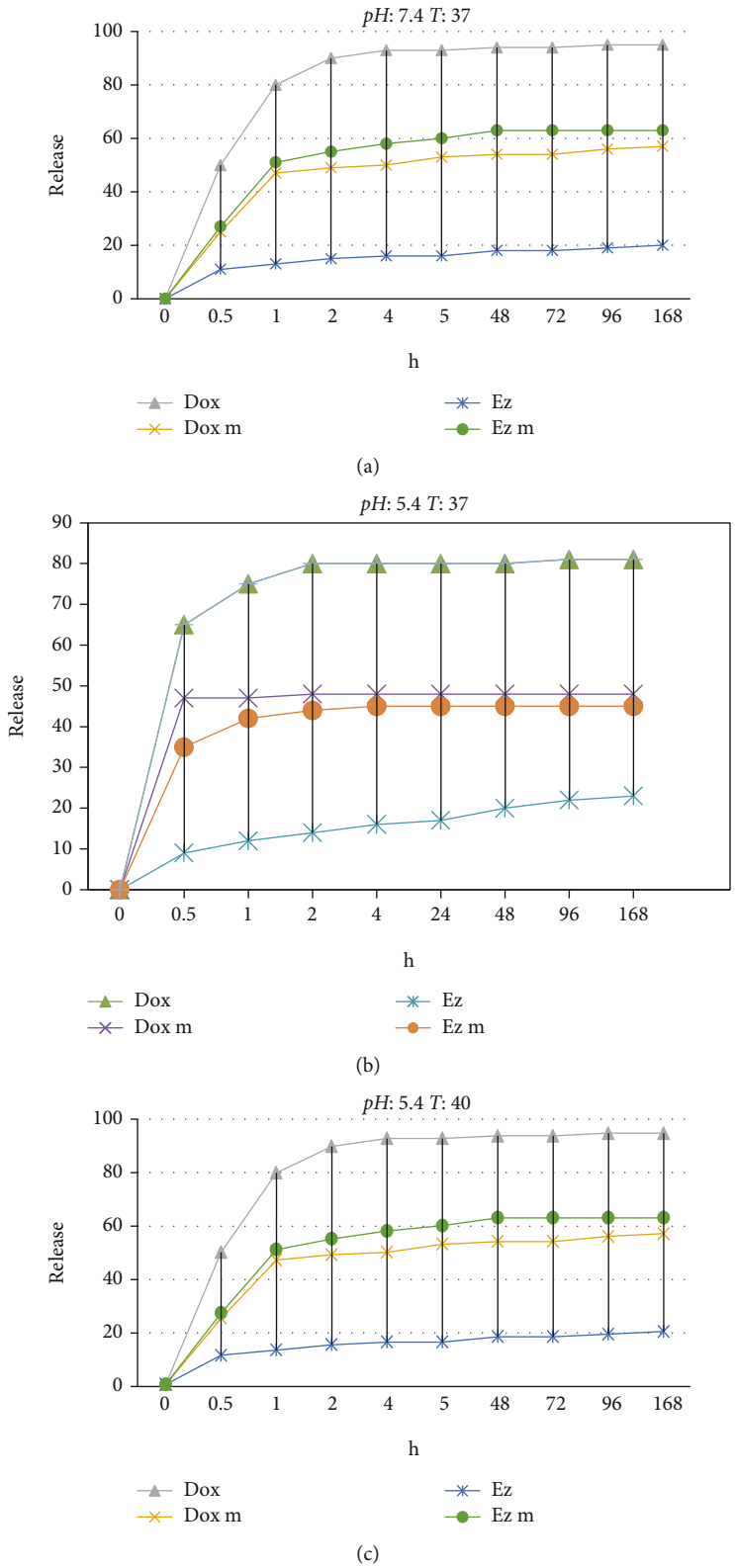


Figure 4: (a) The drug release results from EZ/PU/PCL nanofibers, DOX/PU/PCL nanofibers, and DOX/EZ/PU-PCL nanofibers at pH = 7.4 at 37°C. (b) The drug release results in PU-PCL nanofibers at pH = 5.4 at 37°C. (c) The drug release results from PU-PCL nanofibers at pH = 5.4 at 40°C. Each experiment was performed in triplicate and the values for each point show mean ± SD.

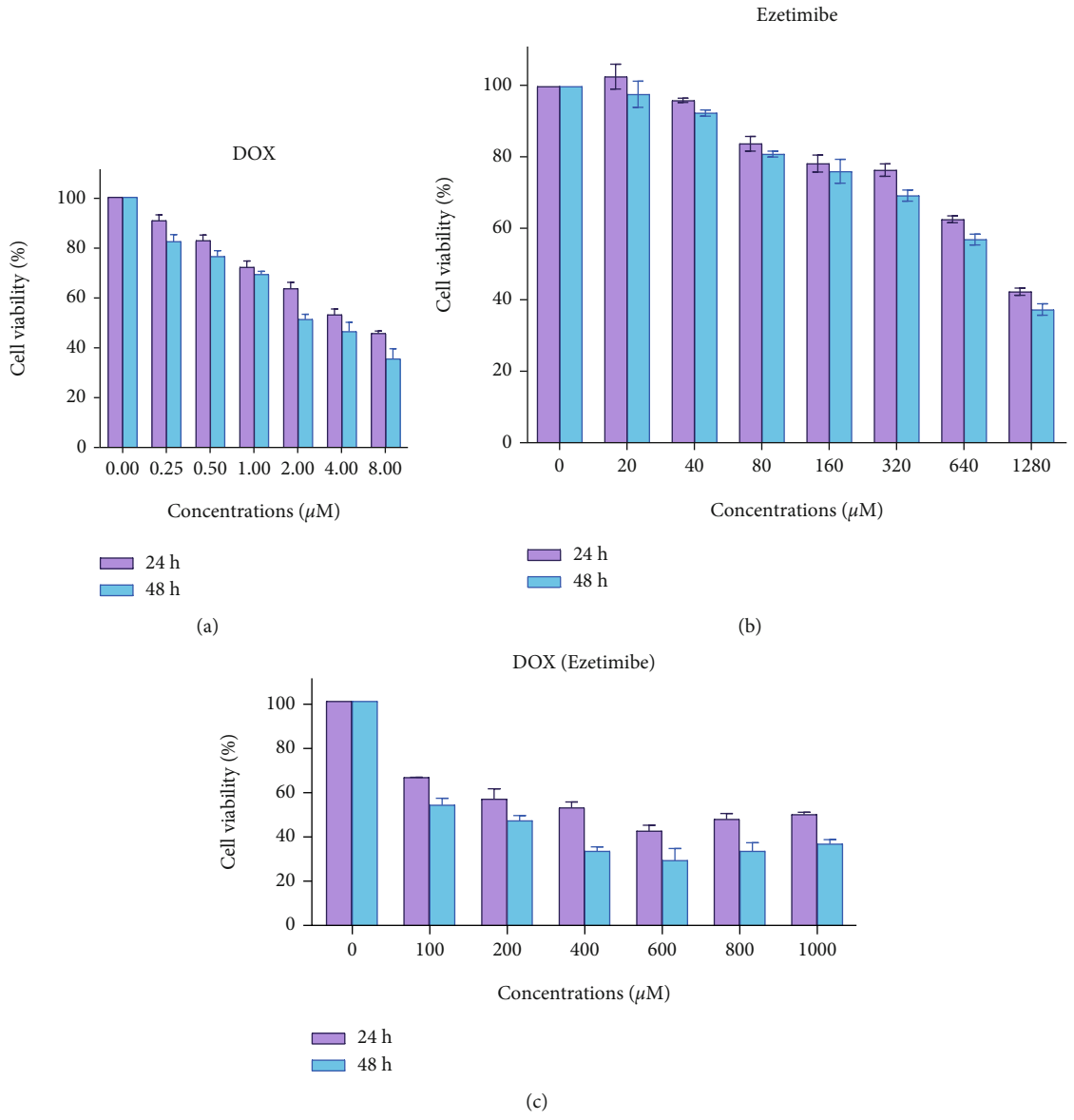


Figure 5: Continued.

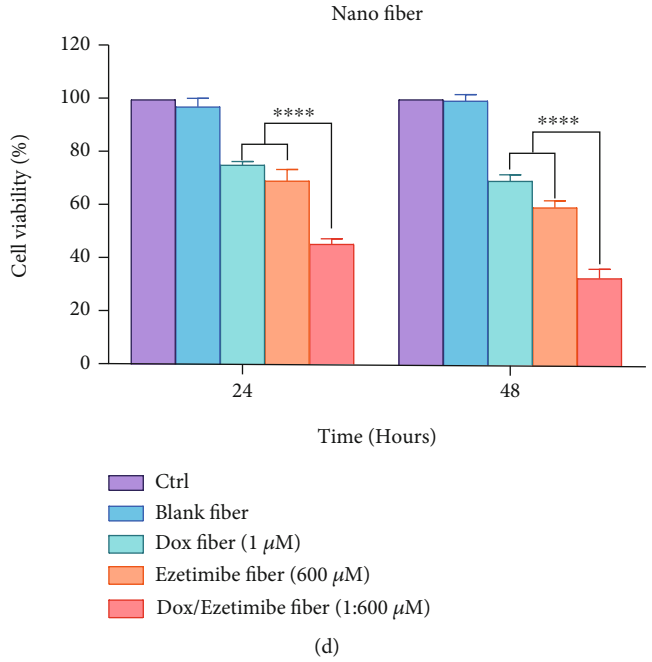


FIGURE 5: PU-PCL polymer elevated the cytotoxicity of DOX and EZ to prostate cancer cells in vitro. (a) The cell viability of PC3 cancer cells was analyzed by MTT methods after treatment with gradient concentrations of DOX for 24 and 48 h. (b) MTT was used to assess the viability of PC3 cancer cells after treatment with gradient concentrations of EZ for 24 and 48 hours. (c) The cell viability of PC3 cancer cells was analyzed by MTT methods after treatment with gradient concentrations of DOX/EZ for 24 and 48 h. (d) The cell viability of PC3 cancer cells was analyzed by MTT methods after treatment with gradient concentrations of DOX/EZ/PU-PCL polymer for 24 and 48 h. $^{****}p < 0.05$. All experiments were conducted in triplicate and data were shown as mean ± SD.

calculate the growth inhibition, a microplate reader (Multiskan MK3, Thermo Electron Corporation, USA) was used to read the optical density of each well at 570 nm. Cell viability percentage was calculated as follows:

$$100 \times \left[\frac{\left(A_{\text{Sample}} - A_{\text{Blank}}\right)}{\left(A_{\text{Control}} - A_{\text{Blank}}\right)}\right], \quad (2)$$

A_{Sample} is the absorbance verified for cells treated with experienced compound, A_{Control} is the absorbance verified for untreated cells, and A_{Blank} is the absorbance verified for blank wells. The tests were achieved in triplicates.

3. Results

3.1. Characterization of Synthesized Nanofibers and Nanoparticles. The chemical structure of the PU-PCL nanofibers was determined with different analytical techniques, including FT-IR, ^{1}HNMR, and SEM.

The SEM images of PU-PCL nanofibers, DOX/EZ-loaded PU-PCL nanofibers, and the fiber diameter distribution are illustrated in Figure 1. It is observed that using the electrospinning procedure under a concentration of 10 wt.% PU-PCL, 1 mL h^{-1} for feeding rate, the ratio of voltage to distance as 25 kV/cm, and collector speed of 1,000 rpm, and the PU-PCL's homogenous nanofibers with an average fiber diameter of 173 nm were formed. Loading DOX/EZ into the PU-PCL nanofibers leads to a gradual increase in the PU-PCL nanofiber diameter to an average size of 443 nm. Also, the diameter of fibers was raised to 443 nm *via* loading the DOX/EZ nanoparticles into the PU-PCL nanofibers. The SEM image of DOX/EZ-loaded PU-PCL nanofibers (Figure 1(b)) revealed that the drugs were loaded successfully on the surface of the nanofibers. The DOX/EZ content over the surface of the nanofibers was 7.5 mg per 100 mg nanofibers.

Another spectroscopic method that confirmed the successful formation of the PU-PCL nanofibers was FTIR. As illustrated in Figure 2(a), the spectra of PU-PCL nanofibers showed peaks at 1219 cm^{-1} (C-O-C stretching) and 1065 cm^{-1} (C-O stretching), which are attributed to the PU structure. Also, peaks at 1452 and 1312 represent the existence of C=C and C-C, respectively. Moreover, a sharp peak that appeared at 1527 cm^{-1} can be associated with the N-H and C-N groups of polymers (Figure 2(a)). The peaks at 1086 cm^{-1} (-C-O-C-), 1219 cm^{-1} (C-O-C), 1726 cm^{-1}, 2830-3024 cm^{-1} (CH_2), and 3433 cm^{-1} (OH) confirm the structure of PCL. Peaks at 1728 cm^{-1} (for C=O), 2830, and 3335 cm^{-1} (for PU) were also captured. The FT-IR spectra of DOX/EZ loaded PU-PCL nanofibers are presented in Figure 2(b), the findings presented peaks at 1612 and 1724 cm^{-1} (C=C and C=O) related to the DOX/EZ structure. The stretching peaks associated with the amide group in the polymer were found at 1612 cm^{-1}. The peak of the carbonyl group in DOX is 1724 cm^{-1} in the cyclohexanone ring and extra DOX dominant peaks overlapped with the polymer (Figure 2(b)).

Figure 3 displayed the ^{1}HNMR spectrum of the PU-PCL. The CH_3 a group from the urethane functionality is found at 1.7 ppm. Aromatic hydrogens give rise to signals at 7.06 to 7.20 ppm (aromatic region). In addition, H_C peaks are observed at approximately 3.34 ppm, and the peak at 5.25 ppm is related to the bicyclic methylene proton of isosorbide.

3.2. Biological Evaluations

3.2.1. Studies on Drug Loading Efficacy and Drug Release. To evaluate the codelivery of Dox and EZ within the nanofibers using the molecules' concentration-based fluorescence intensity calibration, their release profiles were calculated.

The content of DOX and EZ and their loading efficiencies in nanofibers are presented in Table 1. DOX, EZ, and DOX/EZ loaded on nanofiber had drug loading efficiencies (DLE) of 98, 95, and 95%, respectively.

The release profiles of DOX/EZ/PU-PCL nanofibers, DOX/PU-PCL nanofibers, and EZ/PU-PCL nanofibers were assessed in various buffer solutions at pH 5.4 (endosomal environment) at 40°C and pH 7.4 (physiological environment) at 37°C and 40°C. As illustrated in Figure 4, the quick initial release of DOX and EZ from PU-PCL nanofibers was seen within 24 hours, followed by high sustained release rates of DOX/EZ from nanofibers for 7 days. Also, at pH = 5.4 at 40°C, the release of DOX and EZ from PU-PCL nanofibers was greater than at pH = 7.4 at 37°C. The drug molecules' sustained release through the PU-PCL nanofibers was found to last for 48 h, and then, a downreaching equilibrium was found in vitro release kinetics to 168 h.

The release of Dox in the single mode was high, and the release of ezetimibe alone was very low, but in the mixed mode, the release of Dox was less, the release of ezetimibe was more, and their release was almost closer to each other.

3.2.2. Cell Toxicity. The viability of PC-3 cells in DOX/EZ/PU-PCL treatment was assessed by MTT assay. The results of the cytotoxic effects of DOX/EZ loaded nanofibers against PC_3 are revealed in Figure 5. As presented in this figure, cell viability decreases dose-dependently after exposure to single agents like DOX or EZ at various concentrations. Results showed the cytotoxic effects of DOX/EZ-loaded nanofibers (codelivery) were greater than those of nanofibers loaded with a single drug. The results of effect of DOX, EZ, and DOX/EZ/PU-PCL on PC-3 cells are illustrated in Figure 5(c). DOX/EZ/PU-PCL treatment resulted in more cell death at 48 h compared to DOX and EZ with nanofibers (Figures 5(d) and 5(c)). Based on observed results, one may conclude that treating with DOX/EX was more operative compared to DOX or EZ alone.

3.2.3. Statistical Analysis. All experiment was done in 3 repeats, and all data were represented by the mean ± standard deviation (SD). Two-way ANOVA analysis followed by Tukey's post hoc tests was used for statistical analysis with $p < 0.05$.

4. Discussion

The current study's hypothesis was to create an electrospun polyester-urethane nanofiber scaffold that might be used for the codelivery of Dox and EZ. The PU-PCL nanofibers were synthesized and characterized via different methods. The release research findings demonstrated an initial fast release of DOX and EZ after loading the drugs on PU-PCL nanofibers, which might be attributable to drug particles accumulating on the surface of nanofibers. Drug release from nanofibrous mats inside holes and low residual drug content in nanofiber is related to the constant release of pharmaceuticals from nanofiber. The DOX release rate was higher than the EZ release rate in DOX/EZ medicines loaded in PU-PCL nanofibers. Moreover, the highest release rate of DOX was more than that of EZ. The EZ release rate of EZ/PU-PCL nanofibers was relatively slower compared to DOX/EZ/PU-PCL nanofibers, probably due to the diffusion of DOX drug content in loaded DOX/EZ/PU-PCL nanofibers. It is observed that the Korsmeyer-Peppas model (R2 of higher than 0.988) well explained all the DOX and EZ release data obtained from synthesized nanofibers. According to the drug release chart, DOX and EZ releases were high and very low from DOX/PU-PCL and EZ/PU-PCL, respectively. However, the release rates of DOX and EZ are close to each other in mixed release mode and are released along with each other. Investigation into the cytotoxic effects of DOX, EZ, DOX/EZ, and nanofiber on PC-3 cells showed that the cell viability decreased upon exposure to drugs treated with PU-PCL nanofiber after 24 and 48 h (Figure 5(d)). Meanwhile, no cytotoxic effects of the PU-PCL nanofiber alone were found in the PC-3cells. The combination of DOX and EZ showed increased cytotoxicity compared to every single agent at its highest concentrations (the doses that led to 50% of cells being killed in single treatments). Furthermore, when compared to the drug-loaded nanofibers DOX/PU-PCL and EZ/PU-PCL, the sustained release of DOX/EZ from nanofiber was responsible for the highest PC-3 cell mortality after 1 and 2 days.

Drug delivery using nanofiber scaffolds has been reviewed by Mohammadian and Eatemadi [36]. For instance, electrospun PLLA fibers have been used for the delivery of Dox and PTX [37]. Patel et al. [41] attempted to use electrospun fibrous scaffolds as a delivery mechanism for fibroblast growth factors in another investigation (bFGF). In the current work, codelivery of Dox and Ez using PU-PCL nanofiber showed advantages such as sustained release patterns and increasing the cytotoxic effect against cancerous PC-3 cells.

5. Conclusion

In summary, the DOX and EZ were loaded into the PU-PCL nanofibers, and DOX, EZ, and DOX/EZ loaded PU-PCL nanofiber (400 nm average diameter) were created in optimum settings including the voltage of 25 kV and tip-collector distance of 11 cm, solution concentration of 1.5%, and 1 mL/h feeding rate. The sustained TMZ release for 7 days was achieved from DOX, EZ, and DOX/EZ-loaded

PU-PCL nanofibers. Based on our data, DOX and EZ reduce cellular viability at a given dose. Cotreatment of DOX and EZ leads to a decrease in cellular viability compared to each single drug treatment. Based on these results, the DOX/EZ-loaded PU-PCL nanofibers can be used as an appropriate drug delivery implant for delivering DOX and EZ for prostate cancer treatments.

Regarding the continuation of research in this field as a suggestion for future works in this field to achieve the ideal state of controlled drug release, the rate of drug release can be controlled by changing the hydrophilic nature of the polymer. For example, these copolymers can be prepared with different nanoparticles with different and specific percentages, and after the physical or chemical connection of the drug to the polymer body, its hydrolysis rate can be studied. In addition, by using these polymer compounds, it is possible to study and investigate the controlled release of various anticancer drugs with urethane polymers.

And also because the investigation of the role of mitochondria and gap junction proteins and the toxicological concerns of nanogels is not within our scope, it can be investigated in the future.

Abbreviations

DOX: Doxorubicin
EZ: Ezetimibe
PU-PCL: Poly [4,4 methylene bis (phenyl isocyanate)-alt,4 butanediols (propylene glycol) polycaprolactone
DMF: Dimethylformamide
THF: Tetrahydrofuran.

Data Availability

The data used to support the findings of this study are included in the article.

Disclosure

This study was performed as a part of the employment of the authors.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Conceptualization was done by Soodabeh Davaran and Mirzaagha Babazadeh; methodology was done by Fatemeh Rad; formal analysis was done by Fatemeh Rad; data curation was done by Fatemeh Rad; writing—original draft preparation was done by Fatemeh Rad; writing, review, and editing were done by Soodabeh Davaran, Mirzaagha Babazadeh, Abolfazl Akbarzadeh, and Hamidreza Pazoki; project administration was done by Soodabeh Davaran; funding acquisition was done by Soodabeh Davaran, Mirzaagha Babazadeh, Abolfazl Akbarzadeh, and Hamidreza Pazoki.

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References

[1] W. Zhang, X. Zheng, S. Shen, and X. Wang, "Doxorubicin-loaded magnetic nanoparticle clusters for chemo-photothermal treatment of the prostate cancer cell line PC3," *Biochemical and Biophysical Research Communications*, vol. 466, no. 2, pp. 278–282, 2015.

[2] S. Y. Madani, N. Naderi, O. Dissanayake, A. Tan, and A. M. Seifalian, "A new era of cancer treatment: carbon nanotubes as drug delivery tools," *International Journal of Nanomedicine*, vol. 6, p. 2963, 2011.

[3] E. Tsakalozou, A. M. Eckman, and Y. Bae, "Combination effects of docetaxel and doxorubicin in hormone-refractory prostate cancer cells," *Biochemistry Research International*, vol. 2012, Article ID 832059, 10 pages, 2012.

[4] E. Ahmadian, D. Janas, A. Eftekhari, and N. Zare, "Application of carbon nanotubes in sensing/monitoring of pancreas and liver cancer," *Chemosphere*, vol. 302, article 134826, 2022.

[5] R. Salehi, M. Irani, M. Eskandani, K. Nowruzi, S. Davaran, and I. Haririan, "Interaction, controlled release, and antitumor activity of doxorubicin hydrochloride from pH-sensitive P (NIPAAm-MAA-VP) nanofibrous scaffolds prepared by green electrospinning," *International Journal of Polymeric Materials and Polymeric Biomaterials*, vol. 63, no. 12, pp. 609–619, 2014.

[6] M. Norouzi, V. Yathindranath, J. A. Thliveris, B. M. Kopec, T. J. Siahaan, and D. W. Miller, "Doxorubicin-loaded iron oxide nanoparticles for glioblastoma therapy: a combinational approach for enhanced delivery of nanoparticles," *Scientific Reports (Nature Publisher Group)*, vol. 10, no. 1, pp. 1–8, 2020.

[7] K. R. Solomon, K. Pelton, K. Boucher et al., "Ezetimibe is an inhibitor of tumor angiogenesis," *The American Journal of Pathology*, vol. 174, no. 3, pp. 1017–1026, 2009.

[8] E. Ahmadian, S. M. Dizaj, A. Eftekhari et al., "The potential applications of hyaluronic acid hydrogels in biomedicine," *Drug Research*, vol. 70, no. 1, pp. 6–11, 2020.

[9] A. Eftekhari, E. Ahmadian, Y. Azarmi, A. Parvizpur, J. K. Fard, and M. A. Eghbal, "The effects of cimetidine, N-acetylcysteine, and taurine on thioridazine metabolic activation and induction of oxidative stress in isolated rat hepatocytes," *Pharmaceutical Chemistry Journal*, vol. 51, no. 11, pp. 965–969, 2018.

[10] R. Salehi, M. Irani, M. R. Rashidi et al., "Stimuli-responsive nanofibers prepared from poly (N-isopropylacrylamide-acrylamide-vinylpyrrolidone) by electrospinning as an anticancer drug delivery," *Designed Monomers and Polymers*, vol. 16, no. 6, pp. 515–527, 2013.

[11] A. Farboudi, K. Mahboobnia, F. Chogan et al., "UiO-66 metal organic framework nanoparticles loaded carboxymethyl chitosan/poly ethylene oxide/polyurethane core-shell nanofibers for controlled release of doxorubicin and folic acid," *International Journal of Biological Macromolecules*, vol. 150, pp. 178–188, 2020.

[12] S. M. Dizaj, M. Alipour, E. D. Abdolahinia et al., "Curcumin nanoformulations: Beneficial nanomedicine against cancer," *Phytotherapy Research*, vol. 36, no. 3, pp. 1156–1181, 2022.

[13] A. Azadi, M. Hamidi, and M.-R. Rouini, "Methotrexate-loaded chitosan nanogels as 'Trojan Horses' for drug delivery to brain:

preparation and in vitro/in vivo characterization," *International Journal of Biological Macromolecules*, vol. 62, pp. 523–530, 2013.

[14] L. S. del Burgo, R. M. Hernández, G. Orive, and J. L. Pedraz, "Nanotherapeutic approaches for brain cancer management," *Nanomedicine: Nanotechnology, Biology and Medicine*, vol. 10, no. 5, pp. e905–e919, 2014.

[15] S. V. Bhujbal, P. de Vos, and S. P. Niclou, "Drug and cell encapsulation: alternative delivery options for the treatment of malignant brain tumors," *Advanced Drug Delivery Reviews*, vol. 67-68, pp. 142–153, 2014.

[16] H. Amani, H. Kazerooni, H. Hassanpoor, A. Akbarzadeh, and H. Pazoki-Toroudi, "Tailoring synthetic polymeric biomaterials towards nerve tissue engineering: a review," *Artificial cells, nanomedicine, and biotechnology*, vol. 47, no. 1, pp. 3524–3539, 2019.

[17] L. Cheng, C. Wang, L. Feng, K. Yang, and Z. Liu, "Functional nanomaterials for phototherapies of cancer," *Chemical Reviews*, vol. 114, no. 21, pp. 10869–10939, 2014.

[18] M. Salehiabar, H. Nosrati, E. Javani et al., "Production of biological nanoparticles from bovine serum albumin as controlled release carrier for curcumin delivery," *International Journal of Biological Macromolecules*, vol. 115, pp. 83–89, 2018.

[19] M. Prabaharan, "Chitosan-based nanoparticles for tumor-targeted drug delivery," *International Journal of Biological Macromolecules*, vol. 72, pp. 1313–1322, 2015.

[20] L. Yang, S. Gao, S. Asghar et al., "Hyaluronic acid/chitosan nanoparticles for delivery of curcuminoid and its _in vitro_ evaluation in glioma cells," *International Journal of Biological Macromolecules*, vol. 72, pp. 1391–1401, 2015.

[21] S. H. Ranganath and C.-H. Wang, "Biodegradable microfiber implants delivering paclitaxel for post-surgical chemotherapy against malignant glioma," *Biomaterials*, vol. 29, no. 20, pp. 2996–3003, 2008.

[22] M. Irani, G. M. M. Sadeghi, and I. Haririan, "A novel biocompatible drug delivery system of chitosan/temozolomide nanoparticles loaded PCL-PU nanofibers for sustained delivery of temozolomide," *International Journal of Biological Macromolecules*, vol. 97, pp. 744–751, 2017.

[23] B. Ardeshirzadeh, N. A. Anaraki, M. Irani, L. R. Rad, and S. Shamshiri, "Controlled release of doxorubicin from electrospun PEO/chitosan/graphene oxide nanocomposite nanofibrous scaffolds," *Materials Science and Engineering: C*, vol. 48, pp. 384–390, 2015.

[24] K. Qiu, C. He, W. Feng et al., "Doxorubicin-loaded electrospun poly (L-lactic acid)/mesoporous silica nanoparticles composite nanofibers for potential postsurgical cancer treatment," *Journal of Materials Chemistry B*, vol. 1, no. 36, pp. 4601–4611, 2013.

[25] J. Y. Cherng, T. Y. Hou, M. F. Shih, H. Talsma, and W. E. Hennink, "Polyurethane-based drug delivery systems," *International Journal of Pharmaceutics*, vol. 450, no. 1-2, pp. 145–162, 2013.

[26] S.-H. Kuo and P. Kuzma, *Long Term Drug Delivery Devices with Polyurethane Based Polymers and Their Manufacture*, Google Patents, 2010.

[27] C. Akduman, I. Özgüney, and E. P. A. Kumbasar, "Preparation and characterization of naproxen-loaded electrospun thermoplastic polyurethane nanofibers as a drug delivery system," *Materials Science and Engineering: C*, vol. 64, pp. 383–390, 2016.

[28] S. Thandavamoorthy, N. Gopinath, and S. Ramkumar, "Self-assembled honeycomb polyurethane nanofibers," *Journal of Applied Polymer Science*, vol. 101, no. 5, pp. 3121–3124, 2006.

[29] G. R. Da Silva, D. Silva-Cunha, L. C. Vieira et al., "Montmorillonite clay based polyurethane nanocomposite as substrate for retinal pigment epithelial cell growth," *Journal of Materials Science: Materials in Medicine*, vol. 24, no. 5, pp. 1309–1317, 2013.

[30] E. Akbari, H. Mousazadeh, Y. Hanifehpour et al., "Co-Loading of cisplatin and methotrexate in Nanoparticle-Based PCL-PEG System enhances lung cancer chemotherapy effects," *Journal of Cluster Science*, vol. 33, pp. 1751–1762, 2022.

[31] M. Irani, G. M. M. Sadeghi, and I. Haririan, "Gold coated poly (ε-caprolactonediol) based polyurethane nanofibers for controlled release of temozolomide," *Biomedicine & Pharmacotherapy*, vol. 88, pp. 667–676, 2017.

[32] S. S. Qavamnia, L. R. Rad, and M. Irani, "Incorporation of hydroxyapatite/doxorubicin into the chitosan/polyvinyl alcohol/polyurethane nanofibers for controlled release of doxurubicin and its anticancer property," *Fibers and Polymers*, vol. 21, no. 8, pp. 1634–1642, 2020.

[33] R. Manjumeena, T. Elakkiya, D. Duraibabu, A. Feroze Ahamed, P. T. Kalaichelvan, and R. Venkatesan, "'Green' biocompatible organic–inorganic hybrid electrospun nanofibers for potential biomedical applications," *Journal of Biomaterials Applications*, vol. 29, no. 7, pp. 1039–1055, 2015.

[34] E. Ahmadian, A. Eftekhari, H. Babaei, A. M. Nayebi, and M. A. Eghbal, "Anti-cancer effects of citalopram on hepatocellular carcinoma cells occur via cytochrome C release and the activation of NF-kB," *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents)*, vol. 17, no. 11, pp. 1570–1577, 2017.

[35] E. Ahmadian, H. Babaei, A. M. Nayebi, A. Eftekhari, and M. A. Eghbal, "Mechanistic approach for toxic effects of bupropion in primary rat hepatocytes," *Drug Research*, vol. 67, no. 4, pp. 217–222, 2017.

[36] F. Mohammadian and A. Eatemadi, "Drug loading and delivery using nanofibers scaffolds," *Artificial Cells, Nanomedicine, and Biotechnology*, vol. 45, no. 5, pp. 881–888, 2017.

[37] J. Zeng, X. Xu, X. Chen et al., "Biodegradable electrospun fibers for drug delivery," *Journal of Controlled Release*, vol. 92, no. 3, pp. 227–231, 2003.