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Research article

# Fabrication and characterization of hydrocortisone loaded Dextran-Poly Lactic-co-Glycolic acid micelle

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ABSTRACT

A nanomicelle based drug delivery systems is a formulation that can improve the bioavailability and dissolution rate of water-insoluble drugs. In this study, the Dextran-Poly Lactic-co-Glycolic Acid copolymer was synthesized with esterification reaction, confirmed using the fourier-transform infrared spectroscopy and nuclear magnetic resonance. The used method for nanomicelle preparation was nanoprecipitation and the critical micelle concentration value was obtained 10 μg/mL. The particle size of the nanomicelle was less than 100 nm ± 4 nm with narrow size distribution (Polydispersity index = 0.06). Hydrocortisone was loaded to this system. The obtained results for the encapsulation efficiency were 79%, and the drug release was adjusted to a first-order kinetic model with 90% release of drug within the 12 h. The MTT assay showed that even in the high concentration of micelle, the cell viability was remained higher than 90%. Considering the toxicity investigation findings, the Dextran-Poly Lactic-co-Glycolic Acid micellar systems can be suggested as a considerable drug delivery system in hydrocortisone pharmaceutical dosage forms.

## 1. Introduction

Micelles are one type of nanoparticles that are highly regarded in the field of nano-drug delivery (especially hydrophobic drugs), due to their unique physicochemical properties [1, 2, 3]. The micelles consist of a hydrophobic core and a hydrophilic shell so that lipophilic drug is loaded onto the core and prevented from degradation. In addition, they increase the solubility of water-insoluble drugs [4]. Among different types of micelles, polymeric micelles are more widely used in novel drug delivery systems due to their regulatory properties and the convenience of synthesizing these types of micelles in comparison to other micellar carriers [5, 6, 7, 8]. Synthetic and natural polymers are used to synthesize micelles, which should be non-toxic and biocompatible [9, 10, 11]. Dextran is a water-soluble, hydrophilic, and colloidal substance, which is inert in biological systems without any cytotoxicity. Its uses as a carrier for a variety of therapeutic agents including: anticancer, antidiabetics, antibacterial, antiviral, antifungal peptides, drugs, and enzymes have also been investigated [12, 13, 14]. Poly Lactic-co-Glycolic Acid (PLGA) is a copolymer composed of poly glycolic acid (PGA) and poly lactic acid (PLA). Depending on the lactate to the glycolide ratio, there are several forms of PLGA available. PLGA is one of the most successful biodegradable polymers used to enhance nano-drugs due to hydrolysis in the body and produces biodegradable monomers of lactic acid and glycolic acid, which is effectively processed in the body and results in the least systemic toxicity. This polymer is more popular than other biodegradable available polymers due to long-term clinical experience, desirable degradability characteristics, and the potential for use in drug delivery systems [15, 16, 17, 18]. Hydrocortisone is the main glucocorticoid secreted by the adrenal cortex and its synthetic form is used as injectable or topical forms for the treatment of inflammation, allergies and so on. Topical corticosteroids dosage forms, such as hydrocortisone, are absorbed from healthy skin and decrease inflammation or other skin diseases [19, 20]. A limiting factor for the formulation of hydrocortisone pharmaceutical dosage forms is its inadequate solubility in water [19, 20].

The objective of the present study was to design a nanomicelle based drug delivery system containing hydrocortisone. For this purpose, the

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micellar system was prepared from the Dextran-PLGA copolymer. Although the system was previously developed by Jeong et al [21] in this study we tried to achieve a more efficient and appropriate system by making change in the method of preparing micelles and PLGA molecular weight. The size and zeta potential of nanomicelle were evaluated. Then encapsulation efficiency and drug release were investigated and finally the MTT assay was performed to examine the systemic cytotoxicity.

## 2. Experimental

### 2.1. Materials

Dimethylaminopropyl-N′-ethylcarbodiimide (EDC), Dextran (MW ~ 77.0 kDa), PLGA (MW ~ 50–75 kDa) 4-Dimethylaminopyridine (DMAP), N-(3- dry dimethylsulfoxide (DMSO), thiazolyl blue tetrazolium bromide (MTT), dialysis membrane (MWCO = 8000) was purchased from sigma (USA). Dulbecco's Modified Eagle's Medium (DMEM), phosphate buffered saline (PBS, for cell culture), fetal bovine serum (FBS), streptomycin/penicillin, and trypsin were purchased from Gibco (USA).

### 2.2. Preparation of dextran-PLGA copolymer

Copolymer preparation was performed using Jeong *et al.* method with a slight modification [21]. In this method, the coupling between PLGA and dextran was performed through the esterification reaction in the presence of EDC as the dehydrating agent and DMAP as a catalyst in non-water conditions. 1.51 mg PLGA and 350 mg EDC were dissolved in 15 mL dried DMSO at 60 °C. After 30 min, 38 mg of DMAP was added to the solution to activate the PLGA carboxyl group. Then, 680 mg of dextran was slowly added to the solution. The sample was placed in an oil bath at 60 °C for 48 h. After that, the sample was centrifuged at 14800 rpm and 4 °C for 15 min, and the supernatant was placed in a dialysis bag (MWCO = 8000) in a deionized water media for 48 h. The reaction mixture was filtered to remove aggregates and precipitants. The dialyzed solution was lyophilized and then dissolved in 5 mL of dichloromethane three times to remove unreacted PLGA, and then lyophilized again for 24 h. The powder was then dissolved in 5 mL of water 3 times to remove unreacted dextran and lyophilized for 24 h. The synthetic scheme for Dextran-PLGA coupling is shown in Figure 1.

### 2.3. Preparation of hydrocortisone loaded dextran-PLGA micelle

Nanoprecipitation method was used to prepare micelles from the copolymers. For this purpose 20 mg dextran-PLGA copolymer was dissolved in 3 mL dried DMSO. Separately, 2 mg hydrocortisone was dissolved in 2 mL dried DMSO and then added to the dextran-PLGA solution. After that, using a syringe pump, the sample was added at a rate of 0.4 mL/min to 10 mL of deionized water on magnetic stirrer to form the hydrocortisone loaded dextran-PLGA nanomicelle. To eliminate the DMSO, the sample was dialyzed against deionized water for 24 h. The dialyzed solution was then filtered to remove any impurities or probable deposits, and was lyophilized. Dextran-PLGA nanomicelle was prepared by the same procedure described above without drug.

### 2.4. Determination of critical micelle concentration

Iodine was used as the hydrophobic probe to determine the critical micelle concentration. For this purpose, a standard $KI/I_2$ solution was

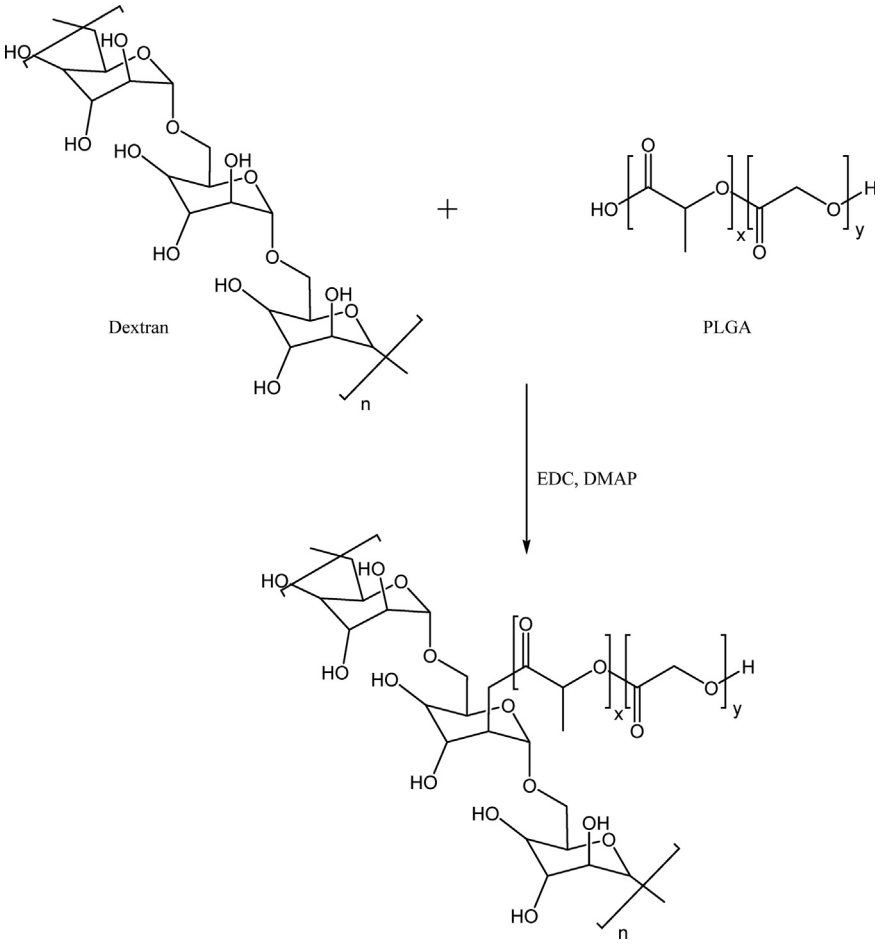


**Figure 1.** Coupling of Dextran to PLGA by estrification reaction using EDC and DMAP.

prepared by dissolving 500 mg potassium iodide and 250 mg iodine in 25 mL of deionized water. A series of dilution of the copolymer in deionized water was prepared and 25 μL of standard $KI/I_2$ solution was added to each sample in the dark condition. The UV absorbance of all the samples was measured at 366 nm and the graph was plotted between the adsorption intensity and the concentration of the micelles. The sharp increase in the absorption of the graph represents the critical micelle concentration.

### 2.5. Characterization studies

#### 2.5.1. Fourier transform infrared (FT-IR) spectroscopy

For the FT-IR test, the Dextran, PLGA, and Dextran-PLGA copolymer were mixed thoroughly with potassium bromide, punched to a tablet employing hydraulic press. The FT-IR data were recorded using the FT-IR spectrophotometer (Irprestige-21-Shimadzu-Japan) at a wavenumber range of 4000 $cm^{-1}$ to 400 $cm^{-1}$.

#### 2.5.2. $^1H$ nuclear magnetic resonance

To the confirmation of structures, the $^1H$ nuclear magnetic resonance (NMR) spectra of compounds in DMSO-*d*6 as a solvent were obtained by a NMR spectrum device (AC-80; Bruker Biospin, Germany).

#### 2.5.3. Size and zeta potential determination

Particle size, zeta-potential, and polydispersity index (PDI) of micelles were analyzed using a Zetasizer (Nano ZS, Malvern Co. Ltd, UK).

#### 2.5.4. Atomic force microscopy

To confirm the size measurement by the DLS, the AFM measurement of micelle was done on a mica plate using ARA-AFM instrument (Ara-Research Co., Iran). Scanning was done in Non-contact mode at scan speed of 1 lin/sec, and scanning area was 5 μm*5 μm and 10 μm*10 μm.

### 2.6. Determination of optimal drug/polymer ratio

Different drug/polymer ratios were used to prepare drug-loaded micelle; the copolymer amounts of 20, 30, 40 mg, and drug amount of 2 mg. Then, the amounts of drug loading in the micelles were determined to investigate the best polymer/drug ratio for optimal drug loading.

### 2.7. Drug content determination

To determine drug content in the hydrocortisone loaded dextran-PLGA micelle, the drug-loaded micelle solution was centrifuged at 14,800 rpm at 4 °C for 30 min. The supernatant was removed and the precipitate containing micelle was dissolved in 20 mL of DMSO. The resulting solution was sonicated 3 times for 2 min to break the micelles. Then the hydrocortisone absorption was measured at 244 nm. The Loading content and Loading efficiency were determined based on Eqs. (1) and (2).

$$\text{Loading contents (\%)} = (\text{drug amount in the micelle}/(\text{amount of polymer} + \text{amount of drug})) \times 100 \quad (1)$$

$$\text{Loading efficiency (\%)} = (\text{drug amount in the micelle}/\text{initial amount of drug}) \times 100 \quad (2)$$

### 2.8. In vitro release studies

In vitro drug release evaluation was done by immersion method. Briefly, one mL Hydrocortisone -loaded micelle solution, equal to 585 μg drug, was transferred to a dialysis bag (MWCO = 8000). The dialysis bag was immersed into 30 mL phosphate-buffered saline (PBS) solution (pH = 7.4) under constant stirring with sink conditions at 37 °C. A control experiment was performed to determine release behavior of free drug. For this purpose 585 μg Hydrocortisone was dispersed in 1ml PBS at pH 7.4. Then, the procedures described for drug loaded micellar system was repeated for control sample. At predetermined time intervals (0.25, 0.5, 1, 2, 4, 6, 8, 12, 24 h) 1 mL aliquot of the medium was withdrawn and replaced with the fresh PBS. Hydrocortisone content was determined in each sample using UV spectrophotometry at 244 nm and calibration curve. All drug-release tests were performed three times.

### 2.9. Cytotoxicity test

The fibroblast cells were obtained from the Pasteur Institute (Tehran, Iran). The cytotoxicities of the dextran-PLGA micelle, hydrocortisone-loaded dextran-PLGA micelle and hydrocortisone were evaluated using an MTT assay. The fibroblast cells were cultured in Dulbecco's modified Eagle's medium (DMEM) with 10% (w/v) FBS, 100 U/ml penicillin, and 100 μg/ml streptomycin. Then, cells were seeded in 96-well plate at a density of $10^4$ cells/well. The cells were grown under a humidified incubator with 5% CO2 at 37 °C until reaching confluency (typically after 24 h). The cells were treated with dextran-PLGA micelle, hydrocortisone -loaded dextran-PLGA micelle and hydrocortisone at concentrations of 50, 100, and 200 μg/ml and subsequently incubated for 24 h. Finally, the MTT solution (5 mg/ml in PBS) was added to each well and incubated for 4 h at 37 °C. The medium with MTT was removed and the formazan crystals formed in the living cells were dissolved in 100 μl DMSO per well. The relative viability (%) was calculated based on the absorbance at $\lambda = 570$ nm using a microplate reader (Molecular Devices Emax, CA, USA). All experimental measurements were collected in triplicate. The values are expressed as the mean ± standard deviation (S.D.) of independent experiments. Data were statistically compared using one-way analysis of variance (ANOVA) and $P < 0.05$ were considered statistically significant. Phosphate buffer was used in control group.

### 2.10. Statistical analyses

All quantitative results were obtained from triplicate samples. Every data point was expressed as mean ± SD. Statistical analyses were carried out by using an unpaired Student's t-test and a value of $p < 0.05$ was considered to be statistically significant.

## 3. Results and discussion

### 3.1. Synthesis and characterization of Dextran-PLGA copolymer

The coupling between PLGA and Dextran was performed through the esterification reaction. In the FTIR spectrum of PLGA (Figure 2), the peak at about 3000 $cm^{-1}$ corresponding for CH, CH2 and CH3 groups. The sharp peak in 1759 $cm^{-1}$ is related to the stretching of the C = O group, while the peak in the 1188 $cm^{-1}$ gave the presence of ether group. The peaks in 1130 $cm^{-1}$ and 1450 $cm^{-1}$ are respectively, related to C–O–C and C–H bonds of the methyl group. For the dextran spectrum (Figure 2), the peak in 3430 $cm^{-1}$ is related to the hydroxyl of polysaccharide group, the peak in 2927$cm^{-1}$ is related to the CH bond, the 1639 $cm^{-1}$ peak is related to carboxyl group, the peak in 918 $cm^{-1}$ is corresponded for alpha-glycosidic bond, the peak in 1153 $cm^{-1}$ gave the evidence for the covalent vibrations of the C–O–C bond and the glycosidic bridge, and the peak in 1018 $cm^{-1}$ is related to the flexibility of the chain around the glycosidic bond α- (1 → 6). In the Dextran-PLGA FTIR spectrum (Figure 2), the peak in the area of 1647 $cm^{-1}$ belongs to the steric group. The presence of this peak shows the successful PLGA coupling to Dextran by the esterification reaction.

The NMR spectroscopy was employed to confirm the copolymer synthesis. This spectrum (Figure 3) showed peaks in the 3–4 ppm region, which is related to Dextran. One peak was observed in the 1.5 ppm region, which is related to the chemical shift of the methyl belongs to PLGA. No chemical shifts indicating the carboxylic acid proton of the

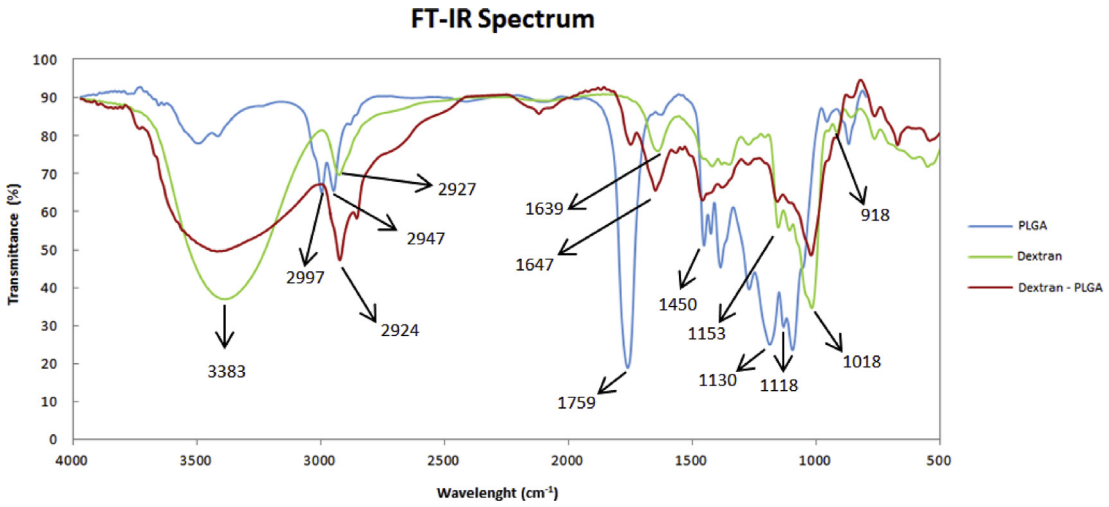


**Figure 2.** FTIR spectrum of PLGA, Dextran, and DEX-PLGA copolymer.

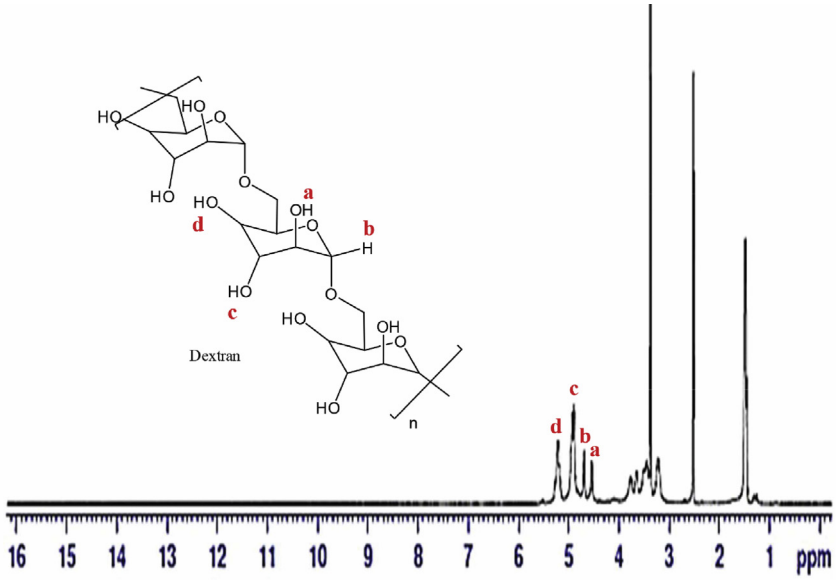


**Figure 3.** $^{1}$H NMR spectrum of Dextran-PLGA copolymer.

PLGA group were observed (about 13ppm). These results indicated a successful PLGA binding to Dextran.

### 3.2. Critical micelle concentration

Figure 4 shows the graph between the absorbance of Iodine in samples in the presence of different concentrations of the copolymer. From the graph, the CMC value was obtained 9.99 μg/mL. It seems that this CMC value is an advantage for the system because smaller CMC caused more stability of micelles in the bloodstream.

### 3.3. Investigation of physicochemical properties of drug loaded micelles

Micelles were prepared by nanoprecipitation method. In this method, organic solution of polymer and drug slowly and dropwise are added the aqueous medium. The gradual increase in the copolymer concentration causes the formation of micelles. In the last step, organic solvent must be removed. Due to the high boiling point of DMSO and the difficulty of removing it through rotary, the dialysis process was used to remove DMSO. This technique was used due to some advantages such as simplicity and obtaining nano particle sizes with narrow size

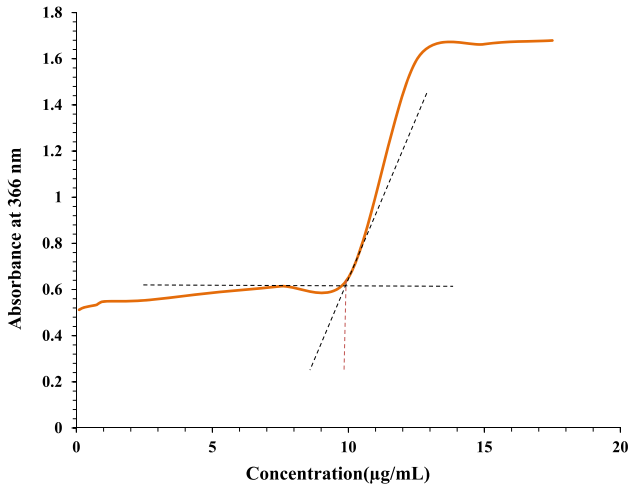


**Figure 4.** Critical micelle concentration (CMC) of the Dex- PLGA micelles obtained using Iodine as hydrophobic probe.

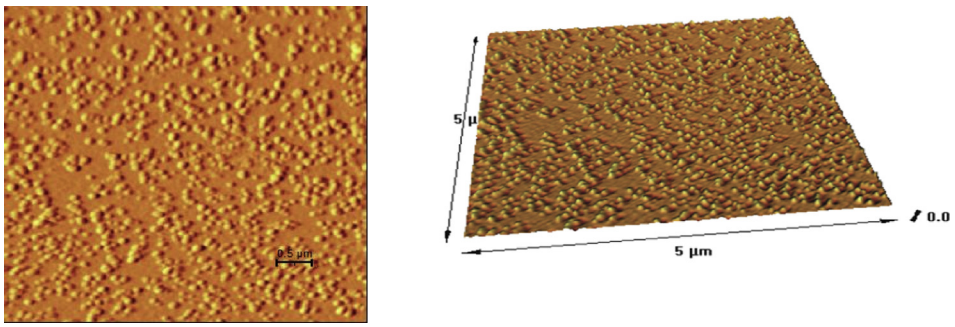


**Figure 5.** AFM images of the Dex-PLGA micelles formed in water.

distribution. It is a recommended method for drug delivery systems fabrication because of ease of scalability, good reproducibility and suitable matching in pharmaceutical industry [22, 23].

Dynamic light scattering (DLS) was used to investigate the size distribution and zeta potential of prepared micelles. The average particle size of micelles was 100.1 ± 3.2 nm (PDI = 0.063 ± 0.021) and the zeta potential was -10.3 ± 0.6 mV. The amount of poly-dispersity index was low, which indicates the uniformity of the size of the micelles. Some works used dialysiss method to nanoparticle synthesis [21, 24]. The results showed that nanoprecipitation method is more suitable for preparing nanomicells than the dialysis bag method resulting smaller particle with very low polydispersity index.

The zeta potential of nanoparticles is one of the most important factors when nanoparticles enter the bloodstream. The positive charge of nanoparticles leads to an increase in the removal of nanoparticles by the reticuloendothelial system and increases adsorption by non-specific proteins [23, 25]. As mentioned above, the zeta potential of the particles was negative. This is due to the OH groups at the surface of dextran.

AFM analysis confirmed the DLS data (Figure 5). As can be seen the micelles appeared to be a spherical shape, and the size was around 70 nm. There is a difference in size between AFM and DLS. The reason is that the DLS measured the hydrodynamic radius of the nanoparticles.

To obtain the optimal drug/polymer ratio, different concentrations of drug and polymer were prepared and their physicochemical properties were compared. As shown in Table 1. The optimum drug/polymer ratio was obtained from 2/20 mg/mg. The loading efficacy obtained for optimal drug/polymer ratio in this study was 79%. The rate of drug loading in drug delivery systems varies depending on some factors such as physicochemical properties of drug and polymer, synthesis procedures, and environmental condition. The effect of PLGA molecular weight on drug loading has been investigated in few studies. Holgado et al. showed that the molecular weight of polymer and end chemical group affects the loading rate of the drug. They demonstrated that the use of high molecular weight PLGA carrying predominantly free carboxylic end groups increases the lidocaine incorporation to the polymeric matrix [26]. The results of present work confirm the Holgado, s claim. The PLGA used in this study has high molecular weight (50–75 Kda). The high loading efficacy can be described by the formation of hydrogen bonds between carboxylic end groups and the drug molecule. More the polymer molecular weight leads more carboxylic functional groups in copolymer core, more chance of hydrogen bonding to drug and consequently more incorporation of drug to polymeric matrix.

### 3.4. In vitro release studies and kinetics evaluation

The results of drug release from Dextran-PLGA micelle in pH 7.4 are shown in Figure 6. The solubility of hydrocortisone in PBS at pH 7.4 is 219.1 µg/ml [27]. The amount of drug in the dialysis bag was 585 µg and the volume of the release medium was 30 ml. Therefore, the highest drug concentration in the release medium would be equal to 585/30 = 19.5 µg/ml. This concentration was less than 21.9 (0.1 drug solubility) and sink condition was stablished.

Drug release from nanoparticles occurs by various mechanisms. In degradable polymeric matrixes, polymer chains Decomposition, resulting in drug diffusion by surface erosion of the matrix. Makadia et al have well explained the mechanism of nanoparticle destruction containing PLGA and drug release from it [28]. In addition in vitro researches have shown that nanoparticles produced by nanopercipitation method are released in two phases: The first phase with burst release of the drug scattered on the surface and the second phase with slowly release of the drug in the nanoparticle core [22]. This mechanism has been confirmed in the present study. The drug release profile indicated that hydrocortisone was released from the nanomicelle in two steps. During the first hours, relatively fast with constant velocity release was observed. In the second phase, the delayed phase, the drug release was slower and lasted for 24 h. After about 8 h from the start of the release, about 80% of the drug was released, and then it would be released slowly. As the molecular weight of PLGA increases, the rate of copolymer degradation will be decreased and it is expected that the drug release rate decreases compared to nanoparticles with the polymer with less molecular weight. But, the high drug loading and the relatively high drug-to-polymer ratio increase the burst release in the first phase and thus increase the overall rate of drug release [28]. Therefore, despite the use of high molecular weight PLGA (50–75 kDa), we were unable to achieve the release of several days which is reported in similar studies [21]. However, the release of the drug from the micellar carrier system is still slowly and in controlled manner in comparison with the free drug.

The release of hydrocortisone in pH 7.4 at 24 h, indicating that the use of nanomicelle in drug delivery causes a slow and long-term release of the drug. This can reduce the drug side effects, the frequency of drug use by patients, and increases their acceptance.

Fitting the drug release data to different release kinetic models showed that considering $R^2$, the drug release from the micellar system probably follows the first-order kinetic model (Table 2). This means that the release of the drug is influenced by its concentration in the system; as

**Table 1.** Determination of optimal drug/polymer ratio.

| Number | Formulation | Drug/Polymer Weight Ratio (Mg/mg) | Loading Contents (%, w/w) | Loading efficiency (%, w/w) |
|---|---|---|---|---|
| 1 | Dextran- PLGA/hydrocortisone | 2/20 | 7.32% | 79% |
| 2 | Dextran- PLGA/hydrocortisone | 2/30 | 4.38% | 68.8% |
| 3 | Dextran- PLGA/hydrocortisone | 2/40 | 2.98% | 61.64% |

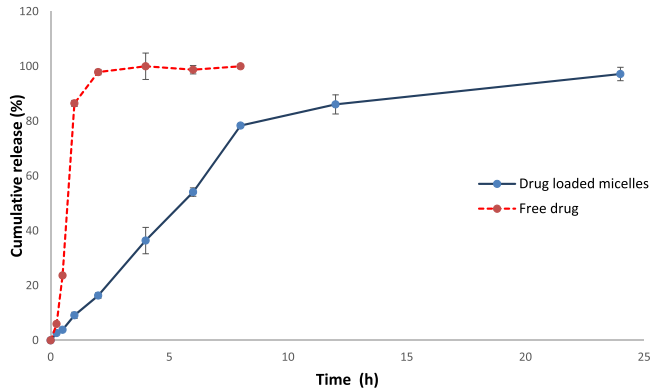


**Figure 6.** Drug release profile from free hydrocortisone, and hydrocortisone-loaded Dextran-PLGA micelles determined using UV spectrophotometry.

**Table 2.** The $R^2$ and release rate equations from in vitro release kinetics.

| Kinetic model | Equation | $R^2$ |
|---|---|---|
| Zero-order | y = 4.3816x+14.085 | 0.7963 |
| First-order | y = -0.0675x+2.0153 | 0.9684 |
| Higuchi | y = 25.307x-11.963 | 0.9324 |
| Korsmeyer–Peppas | y = 1.11105x+.7219 | 0.8066 |
| Hixon | y = 0.1453x+0.1208 | 0.9215 |

the initial concentration of the drug increases, the rate o f release is increased. Although the first-order kinetic of drug release has been used to describe the release of hydrophilic drugs in pharmaceutical dosage forms, it seems that the hydrocortisone entering in the micelles caused to act in the manner of a hydrophilic drug.

### 3.5. *In vitro cytotoxicity studies*

The effects of hydrocortisone on fibroblast cells has been investigated in some researches. In one of these studies, Hein et al showed that glucocorticosteroids inhibit fibroblast proliferation in a dose-dependent manner. Hydrocortisone at the concentration of $10^{-9}$ M after 2 days was ineffective on cell growth [29].

In other work, Longue et al found that hydrocortisone, at concentrations of $10^{-7}$ M and more, reduced cell viability after 48 h [30]. The dose of Hydrocortisone for this experiment in the present work was chosen due to loading rate 50, 100 and 200 µg equal to 1.53 *$10^{-7}$ M, 3.06 * $10^{-7}$ M and 6.12* $10^{-7}$ M. The cytotoxicity of hydrocortisone, Dextran-PLGA micelle, and hydrocortisone-loaded micelles were evaluated against HGF fibroblast cells using MTT assay. As shown in Figure 7, Dextran-PLGA nanomicelle did not have any cytotoxicity even at high concentrations (200 µg/mL), which is indicated that the blank micelles had high biocompatibility. Hydrocortisone has no any effect on the growth of fibroblast cells at concentrations of 50 and 100 µg/mL, but at a concentration of 200 µg/mL of the drug, cellular survival was reduced in the cell line. Hydrocortisone loaded micelles significantly reduced the cytotoxicity of hydrocortisone at a concentration of 200 µg/mL. The beneficial effects of drug-carrying systems on cellular toxicity of various drugs have been reported in studies. Drug delivery systems usually reduce the toxic effects on healthy cells and for anti-cancer drugs, control the release of drug and increase cytotoxicity into cancer cells [31, 32, 33].

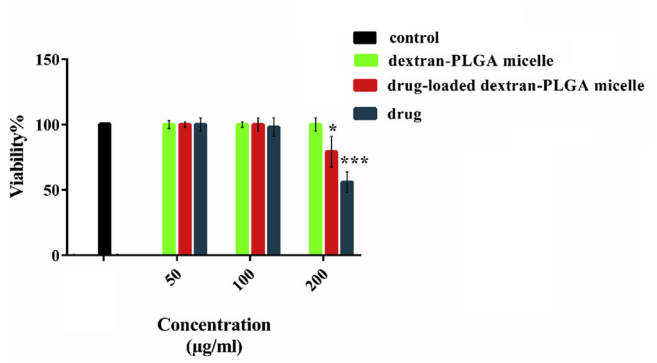


**Figure 7.** Cytotoxicity of hydrocortisone, Dex-PLGA micelle and hydrocortisone-loaded Dex-PLGA micelle determined using MTT assay at 24 h on fibroblast cells. Data are shown as mean ± S.D. The phosphate buffer was used in control group.

## 4. Conclusion

The Dextran-PLGA nanomicelles were prepared as a delivery system for the hydrophobic drug Hydrocortisone. FTIR and HNMR analysis were employed to confirm Dextran-PLGA copolymer forming. The micellar system was synthesized successfully by nanoprecipitation method and the micelles exhibited suitable physicochemical properties. The micelles were in nano size with low polydispersity indicating the uniformity of the size. Given CMC value, the micelles can be formed in low copolymer concentration. Drug loading investigation declared that in optimal drug/copolymer ration, sufficient capacity for drug delivery could be achieved. The drug release from the micellar system was investigated under sink condition. Release behavior of drug showed a controlled manner during 24 h following first-order kinetic in compare with free drug. The use of high molecular weight PLGA has resulted in a high drug loading in the micellar system, but due to the reduction of the polymer to drug ratio, the release time of the drug has been reduced in comparison with some similar researches. Finally, considering the toxicity investigation results, the Dextran-PLGA micellar systems can be suggested as a considerable drug delivery system in hydrocortisone pharmaceutical dosage forms.

## Declarations

### *Author contribution statement*

L. Behbood: Contributed reagents, materials, analysis tools or data; Wrote the paper.

S. Malekhoesseini and A. Rezaie: Conceived and designed the experiments.

S. Khaledian and A. Hosseini: Performed the experiments.

M. Abdoli and M.M. Zangeneh: Analyzed and interpreted the data.

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### *Competing interest statement*

The authors declare no conflict of interest.

### *Additional information*

No additional information is available for this paper.

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