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Biocompatible waterborne polyurethane-urea elastomer as intelligent anticancer drug release matrix: A sustained drug release study

Ali Bahadur[a,*], Aamer Saeed[a,*], Shahid Iqbal[b], Muhammad Shoaib[a], Muhammad Saif ur Rahman[c], Muhammad Imran Bashir[d], Muhammad Asghar[d], Muhammad Asif Ali[d], Tahir Mahmood[e]

[a] Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan
[b] School of Chemistry and Chemical Engineering, University of Chinese Academy of Sciences, Beijing 100049, China
[c] Clinical Research Center, The Second Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310009, China
[d] Department of Physics, Quaid-i-Azam University, Islamabad 45320, Pakistan
[e] Department of Chemistry, Government Postgraduate College, Samanabad, Faisalabad, Pakistan

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ABSTRACT

Waterborne biodegradable polyurethane–urea (WPUU) elastomer is a revolutionary step in the field of green polymer chemistry. In the present study, emulsifier–free biodegradable WPUU elastomer was synthesized by using lysine as an internal emulsifier as well as a chain extender. WPUU elastomer was used as the stimuli–responsive drug release matrix, loaded by cisplatin as a model anticancer drug. Sustained drug release was studied by changing pH (4.4–7.4), drug release medium, and NCO/OH ratio (3–4). Furthermore, significantly inhibitory effect against Sw–620 cancer lines was observed. Highest cumulative drug release of 71.9% was observed at pH of 7.4 in phosphate buffer saline (PBS) by the system having NCO/OH = 3 for 250 h. The oxidative degradation was evaluated in $CoCl_2/H_2O_2$ solution. Mechanical properties were tested by using the mechanical testing machine. The synthesized WPUU films exhibited high thermal stability, hardness, tensile strength and hydrophobicity.

1. Introduction

From the last decade, polyurethanes (PU) have been studied as an interesting class of synthetic polymeric biomaterials due to their excellent mechanical properties, thermoplastic behavior, and biocompatibility [1–3]. Recent advancements of PU are the developments of biodegradable and sustainable products due to exceptional properties such as hydrolytic stability, low *in vitro* protein adsorption and platelet adhesion [4,5]. Many of the biomedical devices such as insulation for pacemakers, prosthetic heart valves, blood pumps, and vessels have been made from PU and are commercially available [6–8]. The key concern is the contact between physiological environment and biomaterials which are the major factor in choosing the proper material for tissue engineering and scaffold in the body [9–12]. Apart from the nature of the application, biocompatibility is a key characteristic which is strongly influenced by the degree of crystallinity, free energy, interfacial concentration of functional groups, polymer surface topography, and surface hydrophilicity [13,14]. That is why developing a biomaterial possessing controlled interaction *in vivo* is a principal emphasis in tissue engineering [15–17]. PU has gained considerable attention and is being widely used in a number of potential biomedical applications like biomedical therapies, drug delivery, biological and membrane science [18–26]. Drug delivery is an important property of these materials and major focus nowadays is on the stimuli–responsive PU which is called as smart (intelligent) systems [27–31]. The PU shows the responses such as shrinking, degradation, or swelling in response to changes in the surrounding. These stimuli can be release media, ionic strength, pH, temperature, and the presence of specific chemical compounds in PU [32–34]. Generally, PUs are prepared from a long chain polyether or polyester diol, a diisocyanate, and a chain extender [35,36]. The specific characteristics depend upon the micro–phase thermodynamic incompatibility between soft segment (SS) and hard segment (HS). SS is long and flexible polyol chain while HS (diisocyanate and short chain diols or diamines) is hard and crystalline [36–41]. The HS works as physical cross–linker because of the hydrogen bonding in between properly arranged HSs [42,43]. Although, many of the articles have focused on the synthesis of solvent based pH–sensitive drug release [43]. Here in this article, we have synthesized water–based PUU elastomer as a sustain drug release system, in response to different release media as well as different pH values. Furthermore, significantly

* Corresponding author.
E-mail addresses: alibahadur138@gmail.com (A. Bahadur), aamersaeed@yahoo.com (A. Saeed).

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inhibitory effect against Sw–620 cancer lines was observed [35,36,44].

2. Materials and method

2.1. Materials

All the chemicals of analytical grade were used in the present study. Polyethylene glycol (PEG, M_n = 2000 g/mol, Sigma), hexamethylene diisocyanate (HDI, ≥ 99.0%, Sigma), triethylamine (TEA, > 99%, Fluka), L–lysine ($C_6H_{14}N_2O_2$, > 99%, Merck), dibutyltin dilaurate (DBTDL, > 97%, Sigma), phosphate buffer saline (PBS, Merck), cisplatin (99.99%, Sigma), fetal bovine serum (FBS, 99%, Fluka), SW-620 colon cancer cells (UAF, Pakistan), MTT assay (99%, Sigma), dimethyl sulfoxide (DMSO, 98.5%, Sigma), deionized water and acetone (C_3H_6O, > 99%, Sigma) were used without further purification.

2.2. Synthesis of WPUU coatings

WPUU was synthesized in a reactor flask, fitted with mechanical stirrer, condenser, dropping funnel, a mantel, and N_2 inlet. Separate solutions of HDI (10.25 g, 61 mmol), PEG (M.Wt = 2000 g/mol, 40 g, 20 mmol), lysine (2.92 g, 20 mmol) were made in dry acetone (20% by *w*/w). The mixture of PEG and lysine solutions were taken in the reactor along with few drops of DBTDL catalyst (100 ppm in acetone). HDI solution was added dropwise under vigorous stirring over 0.5 h at 25 °C and then the resulting mixture was refluxed continuously for 3 h to prepare NCO–terminated PU prepolymer (Pre–PU). Carboxylate ammonium salt of pre–PU was formed by neutralizing pre–PU with TEA (2.8 mL) at 25 °C. 65 mL of deionized water along with lysine (2.92 g, 20 mmol) as a chain extender was slowly poured into resin kettle charged with pre–PU at 25 °C along with strong agitation. The resulting milky emulsion of fully polymerized WPUU was referred as P1 as shown in Scheme 1. The catalyst was not removed after polymerization because it helped to degrade WPUU during sustained drug release study. Similarly, P2 and P3 were synthesized by the same method by changing the NCO/OH ratio. Chemical compositions of all WPUU elastomers are given in Table 1. For different characterizations, WPUU films were formed by casting onto glass Petri dishes and allowing them to dry for 24 h at 60 °C in a vacuum oven.

Table 1
Chemical composition of WDPU coatings.

WPUU	Diisocyanate	Polyol	Chain extender	HDI: PEG: Lys (mmol)	Neutralizing agent	NCO/OH ratio
P1	HDI	PEG	Lysine	61:20:40	TEA	3
P2				71:20:50		3.5
P3				81:20:60		4

2.3. Drug loading

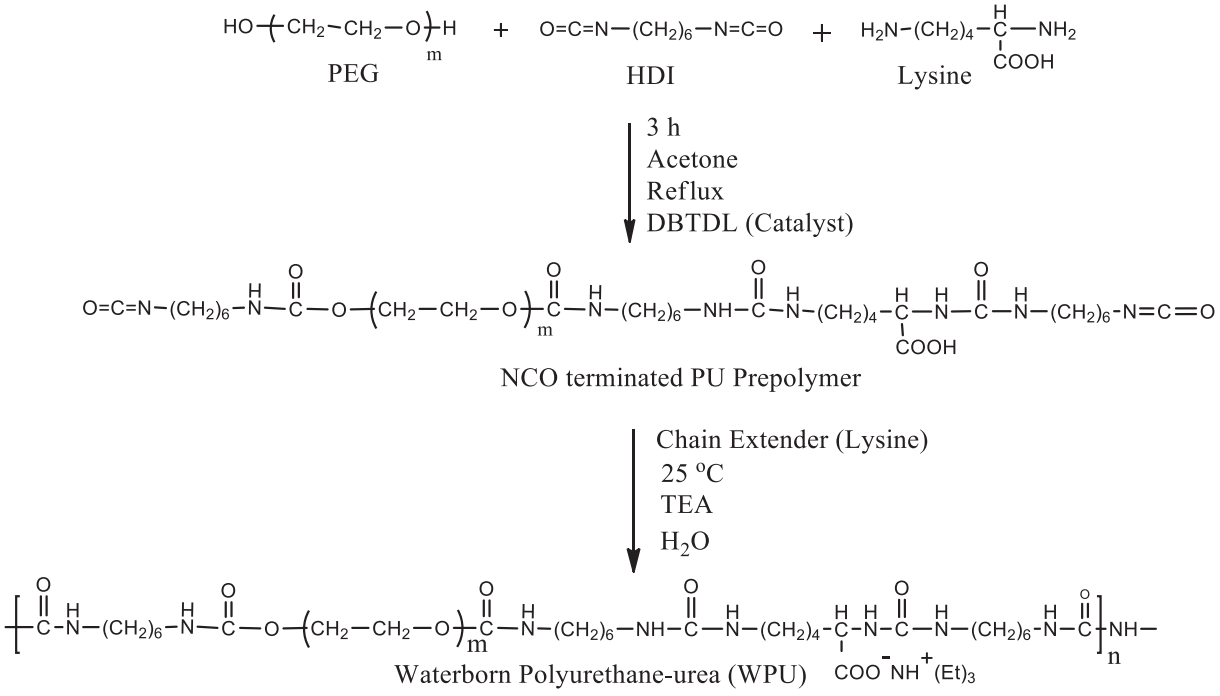
The drug was incorporated into the polymer matrix by solvent evaporation method. The 200 mg of cisplatin was dissolved in 10 mL DMSO. After complete dissolution of the drug, the homogenous solution was poured into 8 g WPUU solution (48% solid contents). The solutions were stirred vigorously for 0.5 h. The final drug loaded WPUU film was formed by pouring drug loaded WPUU solution in a clean Teflon mold (5 cm × 2 cm × 1 mm). It was dried at 70 °C for 4 h in a vacuum oven, then 100 °C till constant weight. The non-embedded drug in WPUU matrix was removed by washing with acetone for several times. Drug effectively embedded in WPUU matrix was determined by measuring drug loading contents (DLC) which were 5.2% (52 mg/g) (Eq. (2)). High drug loading efficiency (DLE) of 96% was achieved, determined by Eq. (3). The resulting drug loaded WPUU films were stored in a desiccator for further use.

$$\text{Drug loading contents}(\%) = \frac{m_{\text{drug loaded}}}{m_{\text{WPUU}}} \times 100 \quad (1)$$

$$\text{Drug loading efficiency}(\%) = \frac{m_{\text{loaded drug}}}{m_{\text{total drug}}} \times 100 \quad (2)$$

2.4. Drug release study

The pre-weighted drug loaded WPUU film was taken in a glass vial, immersed in 10 mL of PBS solution and kept at 37 °C with continuous



Scheme 1. Synthesis of WPUU elastomer.