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Regulating the anticancer drug release rate by controlling the composition of waterborne polyurethane

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ABSTRACT

Water-based polyurethane (WPU) is an alternate green pathway which poses a minimum threat to the environment. In WPU, hard segments (HS) and soft segments (SS) have a pronounced effect on the physicochemical properties of the polymer. Therefore, the effect of a change in the size of HS and SS on the properties of WPU were studied in detailed. Size of HS and SS were varied by increasing the aliphatic chain length of chain extender and PEG respectively. WPU were prepared with different compositions and the effect on thermal stability, mechanical properties, chemical resistance, biodegradation, biocompatibility, the degree of swelling, and drug release rate was studied. For this purpose, two series of WPU were synthesized to study structure–property relationship. The first series of WPU were synthesized by varying molecular weights of polyethylene diol (PEG, M_n = 650, 1250, 1500, and 2000 g/mol) and the second series was synthesized by using diamine chain extenders (CE) with increasing aliphatic chain. All WPU did not show any cytotoxicity as evaluated by MTT assay and are designated as safe biomaterials.

1. Introduction

Polyurethane (PU) is being widely used as an implant material, owing to their biocompatibility and outstanding mechanical properties [1]. Furthermore, it is a versatile polymer for delivering the bioactive substances and therapeutics such anti-inflammatory drugs, antimicrobial agents, and most importantly for delivering the anticancer drugs [2]. As the delivery of most of the anticancer drugs is not controlled, therefore, the effectiveness is limited. The extra dose of the drug can cause severe side effects to the healthy tissues as well [3]. These complications led the scientist to develop new methods for the controlled and site-specific drug release [4]. Therefore, the proposed antidote is the use of such carrier which possesses the controlled release and optimum release profile thus reducing the side effects of the healthy cells and tissues [5]. Many of the external and internal stimuli such as temperature, pH, and voltage have been used for tuning the release of anti-cancer drugs by using the PU carriers [6].

Nowadays polymer industries have developed new synthetic techniques such as waterborne, powder coatings and radiation curable polymers due to the environmental factors [7–9]. The increasing environmental concern, use of volatile organic compounds and solvents are not encouraged in PU synthesis [10]. Therefore, alternate green pathways are being explored and promoted for the synthesis and development of new treatment methods which pose a minimum threat to the environment [11, 12]. Waterborne PU has appreciably replaced solvent-based coatings in order to reduce volatile organic compounds (VOCs) [13]. Aqueous PU was commonly used as adhesives/coatings for various substrates like textile fabrics, leather, plastics, wood, glass fibers, and metals [14]. In this regard, waterborne polyurethane dispersions (WPU) are being currently developed for adhesives, coatings, and biomedical applications [15]. It has been validated that WPU coating possesses better mechanical and adhesive properties as compared to the solvent based PU [16]. WPU comprises linear chains which are thermoplastic and dispersed in water owing to the presence of ionic moieties in their structure which behaves as an internal emulsifier [17]. Generally, WPU properties are associated with the ratio of the soft and hard segment, the degree of phase separation, ionic content, the molecular mass of the macro-diol, the chain size of the chain extender, and the NCO/OH ratio [18]. Therefore, these components and their molecular weights can be varied to have suitable mechanical properties for

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the intended use. In this work, we have fabricated WPUs with the variable structure to control the thermal, mechanical and physico-chemical properties with variable degradation rate [19]. In this work, no external or internal stimuli was used for controlling the release of the drug, rather it is controlled by using the suitable carrier according to the demand.

2. Materials and method

2.1. Materials

Hexamethylene diisocyanate (HDI, ≥ 99.0%, Sigma), Poly(oxyethylene) glycol (PEG, M_w = 650, 1250, 1500, 2000 g/mol, Sigma), 1,2-diaminoethane (1,2-DAE, > 99%, Sigma), 1,6-diaminohexane (1,6-DAH, ≥98.5%, Sigma), 1,8-diaminooctane (1,8-DAO, ≥98.5%, Sigma), 1,4-diaminobutane (1,4-DAB, ≥98.5%, Sigma), L-lysine ($C_6H_{14}N_2O_2$, > 99%, Merck), triethylamine (TEA, > 99%, Merck), and dibutyltin dilaurate (DBTDL, > 97%, Sigma) were used as such without further purification for the synthesis of WPU. MTT assay kit, 5-fluorouracil (5-FU, 99.99%, Sigma), normal human fibroblast cells (NHFB, AUF Pakistan), phosphate buffer saline (PBS, ≥97.5, Daejung) were used for drug release studies and cytotoxicity evaluation.

2.2. Synthesis of biocompatible waterborne polyurethane elastomer

WPU was synthesized by two steps process. In the first step pre-polyurethane (pre-PU) was prepared, which was further polymerized by the reaction with chain extender (CE) to form fully polymerized WPU. Briefly, the solutions of PEG (20 mmol) and L-lysine (20 mmol) in acetone were taken in the reactor flask along with 0.5 mL of 1% (*w*/w) DBTDL. HDI (61 mmol) solution was added dropwise under vigorous stirring at room temperature and the mixture was refluxed for 3 h to prepare NCO-terminated pre-PU. Pre-PU was converted into carboxylate ammonium salt by neutralizing it with TEA (2.8 mL). This carboxylate ammonium salt was stirred with ethylenediamine (20 mmol in 65 mL of deionized water) as a CE, to get final WPU (Fig. 1). Similarly, other WPUs (P5–P10) were synthesized by the same method by changing the molecular weight of PEG (650 to 2000 g/mol) and the chain length of CE, respectively (Fig. 1). Chemical compositions of all WPU elastomers are given in Table 1. For different characterizations, WPU films were formed by casting onto Petri dishes and dried for 24 h at 60 °C in a vacuum oven.

2.3. Drug release studies

The drug was loaded physically into the polymer matrix before the film forming process. The 200 mg of 5-fluorouracil in 10 mL DMSO was added, stirred and sonicated with the 10 g P4 solution (47.1% solid contents). Drug-loaded WPU film was formed by pouring this mixture into Teflon moulds (5 cm × 2 cm × 1 mm) and drying till constant weight at 60 °C. The nonembedded drug on the surface was removed by washing with acetone. Drug effectively embedded in the WPU matrix was determined by measuring drug loading contents (DLC) which were 4.2% (Eq. 1). High drug loading efficiency (DLE) of 97.6% was achieved, determined by Eq. 2. Drug release was studied by using these drug-loaded WPU films by immersing them into 10 mL PBS solution at 37 °C along with stirring at 50 rpm. The concentration of released drug was determined after specific time intervals by taking 1 mL PBS solution from this mixture and the same amount of fresh PBS was added to maintain the original PBS volume of 10 mL. The concentration of drug in solutions taken out from the vial was determined by using UV/Vis spectrometer. Each experiment was performed thrice, and the average value was reported.

$$Drug\ loading\ contents\,(\%) = \frac{m_{Loaded\ Drug}}{m_{WPU}} \times 100 \quad (1)$$

$$Drug\ loading\ efficiency\,(\%) = \frac{m_{Loaded\ drug}}{m_{Total\ drug}} \times 100 \quad (2)$$

2.4. Cytotoxicity test

Inhibitory effect of WPU against normal human fibroblast (NHFB) cell lines was evaluated by using MTT assay. First, 1 × 10^5 cells were seeded in 96-well plate under optimum conditions using 10% FBS incubated at 37 °C in 5% CO_2 and then treated with different concentrations of WPU and WPU-5FU (0, 25, 100, 400, and 800 μg/mL).

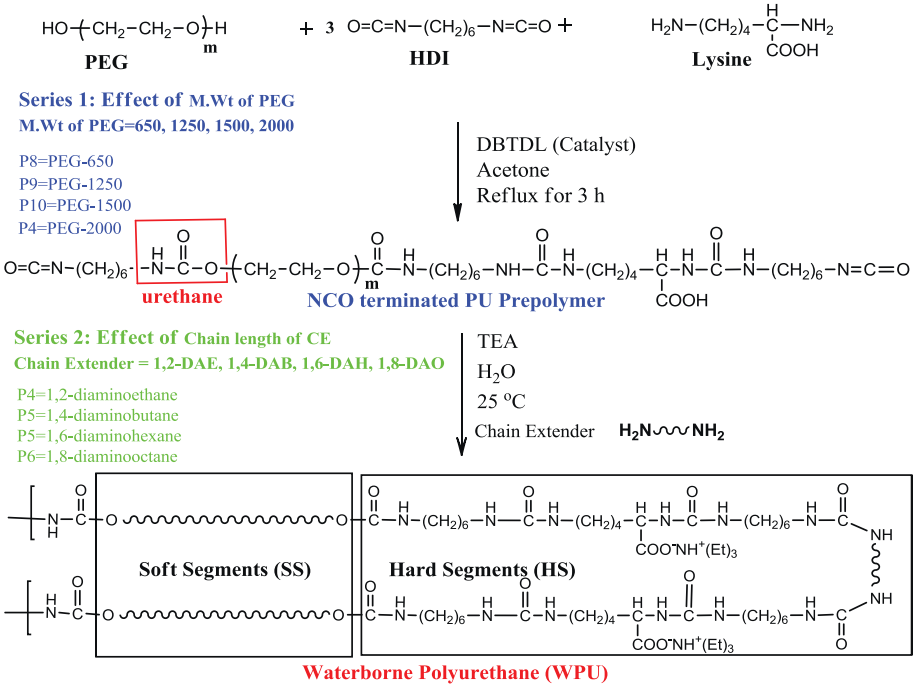

Fig. 1. Synthesis of waterborne polyurethane (WPU).