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Relationship of hard segment concentration in polyurethane-urea elastomers with mechanical, thermal and drug release properties

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ABSTRACT

The main aim of this research was to study the effects of size and concentration of the hard segments on thermal stability, solvent resistance, hardness and drug delivery applications in polyurethane-urea (PUU) elastomers. Four diamines having different aliphatic chains, were synthesized and used as chain extenders (CE) to synthesize PUU. NCO/OH ratio was changed from 2-2.5 to study the effect of concentration of hard segments. Structure, morphology, thermal stability, hardness, solvent resistance, drug delivery and mechanical properties of polyurethane-urea elastomers were examined by means of fourier transform infrared spectroscopy (FTIR), wide-angle X-ray diffraction (WAXD), thermogravimetric analysis (TGA), shore durometer, UV/Vis spectrophotometer and universal testing machine (UTM) respectively.

1. Introduction

In recent years, the polymers whose structure and conformations change in response to certain external stimuli, such as pH [1], light [2], electric potential [3], magnetic field [4] and temperature [5] have attracted considerable attention as smart materials [6]. Polyurethanes (PU) are among interesting biomaterials and are also being used in a variety of implantable medical devices [7]. It is a biocompatible polymer with low cytotoxicity which makes it the potential candidate for applications in tissue engineering, material science, and drug delivery [8]. This low cytotoxicity of PU is due to its low protein adsorption property. However, aliphatic isocyanate and aliphatic diamine chain extenders based PU show low biocompatibility and high toxicity due to high protein adsorption [9]. Polyurethanes are important biomaterials, widely used for stimuli-responsive controlled drug release studies because of hydrolytic stability, low in vitro protein adsorption and platelet adhesion [10]. However, the major concern has been the fast and poorly controllable release rates of polymers based drug carriers [11]. To address these issues biocompatible polyurethanes characterized by the alternation of hard and soft segments were synthesized in order to modulate the degradation rate and release profile [12]. Polyurethane-urea (PUU) elastomers are the multi-block copolymers, having thermodynamic incompatibility between soft and hard segments due to their two-phase morphology [13]. There can be various sorts of soft segments, such as polyester or polyether macro glycol, whereas the hard segment is formed by extending an aromatic or aliphatic diisocyanate with less molecular weight diamine [14]. Owing to the incompatibility between soft and hard phases, PUU elastomers exhibit exceptional properties of high elasticity, extra toughness, and huge tensile strength [15,16]. PUU have the superior degree of micro phase separation due to greater cohesive forces in urea linkages as compared to PU elastomers [17,18]. Therefore, PUU elastomers have improved mechanical and thermal characteristics than those of conventional PU [19]. However, both of these exhibit poor thermal resistance and mechanical

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properties deteriorate from 80 to 90 °C, which significantly confine their use at high temperature, but appropriate to be used in bio-applications [20]. It is well-known that the structure of chain-extender has a significant effect on PUUs and PUs, so effects of chain-extenders on the structure, morphology, and properties of PUUs were studied extensively. Actually, increase in NCO/OH ratio caused a rise in hard segment domain concentration [21]. The increase in the size of chain extender causes amplification in length of hard segments domain which increases the size due to greater physical cross-linkage of hard segments.

In continuation of our previous work [21,22], here in this study, the dependence of the structural, surface, thermal, sustained drug release and mechanical properties of polyurethane urea elastomers on the length, concentration, and structure of chain extenders have been extensively studied. Especially the effect of increasing aliphatic chain length of chain extenders on drug delivery. To our knowledge, this relationship between the concentration of hard segment and drug release has not been studied previously.

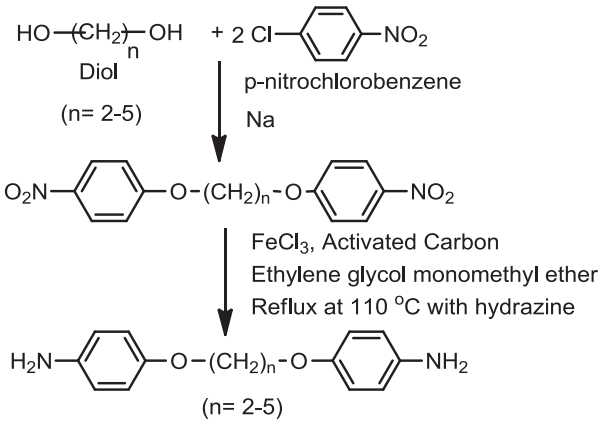
2. Materials and method

2.1. Materials

The chemicals, reagents, and solvents used in this study were of analytical grade, obtained from Sigma-Aldrich, Germany, used without further purification. These include; toluene diisocyanate (TDI, ≥99.0%), polyethylene glycol (PEG, M_n = 2000 g/mole), ethylene glycol (MEG, ≥98.5%), 1,3-propane diol (PDO, ≥98.5%), 1,4-butane diol (BDO, ≥98.5%), 1,5-pentane diol (PTDO, ≥98.5%), chlorobenzene (97.5%), sulphuric acid (H_2SO_4, 18 M), nitric acid (HNO_3, 15.9 M), sodium sulphate (Na_2SO_4, 97.5%), sodium carbonate (Na_2CO_3, ≥99%), sodium metal, activated carbon, ethylene glycol monomethyl ether, hydrazine monohydrate ($N_2H_4 \cdot H_2O$, 85%), *n*-hexane (C_7H_{16}, 99%), ferric chloride ($FeCl_3 \cdot 6H_2O$, 95%), hydrochloric acid (HCl, 12.1 M), ammonia solution (NH_4OH, 28%), 1,4-dioxane (99.9%), *N*,*N*-dimethyl formamide (DMF, 99%), potassium carbonate (K_2CO_3, 98.5%), methanol (CH_3OH, 95%), and ethanol (C_2H_5OH, 95.5%), acetone (C_3H_6O, > 99%), phosphate buffer saline (PBS, 97.5%), ciprofloxacin (99.99%), tetrahydrofuran (THF, 97.5%), chloroform ($CHCl_3$, 99%), dimethyl sulphoxide (DMSO, 97%) and carbon tetrachloride (CCl_4, 99%).

2.2. Synthesis of chain extenders

A round bottom flask was charged with ethylene glycol (3.1 g, 50 mmol) and sodium metal (2.3 g, 100 mmol) at room temperature. Solution of *p*-nitrochlorobenzene (15.7 g, 100 mmol) in toluene (1:1) was added dropwise to the reaction flask with refluxing for 4 h. Brown precipitates of 1,2-di(*p*-nitrophenoxy) ethane were appeared which were further reduced to 1,2-di(*p*-aminophenoxy)ethane by refluxing at 110 °C for 8 h with $N_2H_4 \cdot H_2O$ (20 mmol), activated carbon (0.5 g), $FeCl_3 \cdot 6H_2O$ (1.0 g), and ethylene glycol monomethyl ether solvent (150 mL). When white precipitates appeared, excess hydrochloric acid was neutralized by adding ammonia (20%) until the pH becomes 11–12. The precipitates of 1,2-di(*p*-aminophenoxy)ethane were washed several times with distilled water, then re-crystallized with ethanol. Crystals were dried at 60 °C in a vacuum oven to constant weight of product. Similarly other chain extenders such as 1,3-di(*p*-aminophenoxy)propane (DAPP), 1,4-di(*p*-aminophenoxy)butane (DAPB) and 1,5-di(*p*-aminophenoxy)pentane (DAPPT) were prepared by using propylene glycol, butylene glycol and pentane glycol respectively instead of ethylene glycol by the above-described method [21]. (see Scheme 1).



Scheme 1. Synthesis of aromatic diamine chain extenders from aliphatic diols.

2.3. Synthesis of PUU elastomers

TDI (17.4 g, 100 mmol) was weighed into a 250 mL three-necked round-bottom flask equipped with mechanical stirrer, dropping funnel, and nitrogen inlet. Pre-dried PEG (100 g, 50 mmol) was added to the reaction flask with stirring over a period of 0.5 h at 70 °C on the oil bath. The mixture was further heated at 70–80 °C for 2 h with stirring to obtain NCO-terminated PU pre-polymer [23]. This pre-polymer was reacted with chain extenders, (50 mmol) in 1,4-dioxane at 70 °C for 0.5 h and as depicted in Scheme 2. The mixture was poured into Teflon molds and kept at room temperature for 24 h to evaporate all the solvent. For the curing purpose, these thin films, were kept for 3 h in the vacuum oven at 60 °C [21].

2.4. Drug loading

Ciprofloxacin was loaded to PUU films by solvent evaporation method. A known weight of ciprofloxacin was added in the polymer solutions to prepare 5% w/w of the PUU films. This mixture was sonicated for 2 h for complete homogenization. This solution was then poured into Teflon molds of 5 cm × 2 cm × 1 cm. It was kept in a vacuum oven at 100 °C for 48 h and then 110 °C for further 24 h till constant weight. These films were put in a desiccator for further use. The obtained PUU films were loaded with 5% w/w of ciprofloxacin [16].

2.5. Characterizations

FTIR spectra were taken by using a thermo nicolet FTIR (4000–400 cm^{-1}, resolution 2 cm^{-1}, 32 scans per measurement) to which thermo nicolet cell was attached. TGA/DTG curves were taken by using thermogravimetric analyzer, Q 500, TA instruments USA. Hardness was measured by using digital manual hardness check shore D, Gibitre instruments Sri Lanka. Stress-strain curves were obtained according to the ISO 527 method with cross-head speed of 200 mm/min by using universal testing machine from Zwick GmbH, Ulm Germany. X-ray diffraction (XRD) analysis by using an X-ray diffractometer (PANalytical, X′ Pert Pro, Almelo, Netherlands); Cu Kα was used as a source of radiation. It was operated at 40 kV with 2θ value varying from 5 to 70. UV/Visible spectrophotometer (Shimadzu UV-265) was scanned from 200 to 700 nm for determining the concentration of ciprofloxacin drug. Ciprofloxacin drug has a UV absorption spectrum with λ_{max} of 271 nm and concentration of all the samples were calculated at this wavelength.