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Biomechanical studies on aliphatic physically crosslinked poly(urethane urea) for blood contact applications

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Abstract Hydrophobic and physically crosslinked (virtually crosslinked through hydrogen bonding) aliphatic poly(urethane urea)s were developed and characterized for its biomechanical properties. The aging under induced-stress (bend samples) condition reveals resistance of poly(urethane urea) to environmental stress corrosion cracking (ESC) in hydrolytic media, Ringer's solution and phosphate buffered saline at 50°C. The strain-induced (20% tensile strain) and aged polymer in hydrolytic enzyme medium, papain and in buffer reveals increase of elastic modulus in papain enzyme and papain buffer. The increase of elastic modulus is attributed to unidirectional reorganisation of chains under continually strained conditions. The polymer exposed in boiling alcoholic potassium hydroxide solution (accelerated hydrolytic chemical degradation) reveals no degradation. A comparative evaluation of poly(ether urethane urea)s reveals inferior properties. Poly(ether urethane urea)s polymer undergo hydrolytic degradation in boiling alcoholic potassium hydroxide solution. The candidate poly(urethane urea) HFL 18-PUU is more promising elastomer for long-term biomechanically sensitive blood contact applications such as heart valve and blood pump diaphragm of left ventricular assist device.

1 Introduction

Polyurethane elastomers have been used extensively in biomedical applications. Poly(ether urethane)s have proved sufficient biocompatibility in a variety of blood contact applications such as experimental artificial hearts, left ventricular assist devices [1] and blood pumps [2]. However these polyurethanes could survive only for short-term. The failure of these clinical devices is mainly due to catastrophic failure of the polyurethane material used in these devices. Though polyurethane has been used in the development of cardiac pacemaker, failure of polyurethane-coated pacing leads has been reported during long-term use [3]. Biodegradation induced by hydrolytic, oxidative and environmental stress corrosion mechanism leads to catastrophic failure of medical devices. Mammary prostheses developed from aromatic toluene diisocyanate based polyurethane degraded, during long-term implantation. Surgiteck® have met court litigation for the clinical failure of these mammary prostheses. Aromatic polyurethanes based on diphenyl methane diisocyanate (MDI) undergo thermal and thermohydrolytic degradation under prolonged and/or repeated autoclaving conditions producing methylene dianiline (MDA), a suspected carcinogen [4, 5]. Jayabalan et al. [6, 7] have developed aliphatic and cross-linked polyurethanes based on hexamethylene diisocyanate (modified) for long-term tissue contact applications.

Polyurethanes used as vital components in biomechanically sensitive blood contacting devices such as pump membrane of blood pumps and flexible leaflet of artificial hearts and left ventricular assist devices have to undergo repeated cyclic flexion [8]. Therefore it is essential to

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develop low elastic modulus polyurethane with reduced bending stress and increased fatigue life. Moreover low elastic modulus polyurethane allows membrane to flex more freely without producing adverse changes in blood flow [9]. In addition to the requirement of low elastic modulus, biodurability of the polyurethane in biomechanical environment is therefore a mandatory requirement for use in biomechanically sensitive blood contact applications.

The present paper deals with the evaluation of biomechanical-induced biodegradation of novel virtually crosslinked poly(urethane urea)s for blood contact applications.

2 Materials and methods

2.1 Synthesis and characterization of poly(urethane urea)

Novel poly(urethane urea)s (HFL9-PUU, HFL13-PUU HFL18-PUU HFL15 PU) were synthesised using methylene bis (*p*-cyclo hexyl isocyanate) $H_{12}MDI$, hydroxy terminated poly butadiene (HTPBD) and 1,6 hexa methylene diamine (HDA) by two step solution polymerisation method. Poly(ether urethane urea)s (HFL16-PEU and HFL17-PEU) were also synthesised for the comparison of properties using mixed polyols, HTPBD and poly tetramethylene glycol (PTMG) along with above reactant. The detailed conditions of the synthesis were published elsewhere [10–12]. The composition of the hard and soft segments is given in Table 1. The molten polymer was cast in a glass plates and cured. The cured polymer sheet was purified and freed from sol fraction by Soxhlet extraction and characterized.

2.1.1 FT-IR spectral analysis

The new polymers were analyzed by the Fourier transform infrared spectrophotometry (FT-IR) using ATR accessory. The clean polymer sheet was sandwiched in a KRS-5 ATR crystal and the IR spectrum was recorded. A Nicolet impacts 410 FT-IR spectrophotometer was used.

Table 1 Chemical composition of polymers

Polymer	Hard segment (mol%)	Soft segment (mol%)
Poly(urethane urea)		
HFL9-PUU	H_{12}MDI-HAD (57.5)	HTPBD (42.5)
HFL13-PUU	H_{12}MDI-HAD (67.9)	HTPBD (32.1)
HFL18-PUU	H_{12}MDI-HDA (75.0)	HTPBD (25.0)
HFL15-PUU	H_{12}MDI-HDA (80.0)	HTPBD (20.0)
Poly(ether urethane urea)		
HFL16-PEU	H_{12}MDI-HDA (57.5)	HTPBD-PTMG (42.5)
HFL17-PEU	H_{12}MDI-HDA (67.9)	HTPBD-PTMG (32.1)

2.1.2 Wide angle X-ray diffraction studies

The wide angle X-ray diffraction studies were carried out at room temperature using a Siemens unit (Siemens, X-ray diffractometer D 5005). Nickel filtered Cu K_α radiation was used for obtaining X-ray diffractograms. The circular sheets of polymers were used for the measurement of diffraction angle corresponding to the crystallites. WAXD spectrum is obtained as plot of intensity against angle of diffraction in 2θ scale.

2.1.3 Determination of molecular weight between crosslinks

The number average molecular weight between crosslinks (M_c) was determined by swelling experiments. Initially the swelling coefficient was determined by subjecting the polymer sheet to attain equilibrium swelling in different solvents with different solubility parameters. The solvent in which the polymer showed maximum swelling was used for determining the swelling coefficient (Q). In the present polymers, maximum swelling was observed in tetrahydrofuran (THF). Therefore, the accurately weighed polymer materials were allowed to swell in it for 2 days and the increase in weight was measured. The swelling coefficient is the ratio of volume of solvent in the swollen polymer to that of dry polymer and is defined by the relation:

$$\text{Swelling coefficient } (Q) = \frac{\text{Weight of the solvent in swollen polymer}}{\text{Weight of the swelled polymer}} \times \frac{\text{Density of polymer}}{\text{Density of solvent}}$$

The volume fraction of the polymer in the swollen polymer (V_r) was calculated from swelling coefficient. The solubility parameter of that solvent (δ_s) which imparts maximum swelling was taken as the solubility parameter of the polymer (δ_p). The crosslink density (γ) of swollen polymers (density of virtual or pseudo crosslinks due to extensive hydrogen bonding) was determined by using modified Flory–Rehner's equation. The number average molecular weight between crosslinks (M_c), which is the reciprocal of apparent crosslink density (mol/cm^3), was also calculated.

$$\gamma = \frac{-(V_r + \chi V_r^2 + \ln(1 - V_r))}{d_r V_o (V_r^{1/3} - V_r/2)} = \frac{1}{M_c}$$

where $V_r = \frac{1}{1+Q}$ is the volume fraction of the polymer in the swollen polymer, χ the polymer–solvent interaction parameter = lattice constant 0.34 for ($\delta_s = \delta_p$), V_o the molar volume of the solvent (cm^3/mol), and d_r is the density of the polymer (g/cm^3).

2.1.4 Measurement of contact angles

The degree of hydrophobicity was determined by contact angle measurements. Contact angle with water, an indicator of the wettability of surface was measured by sessile drop method using an optical bench type goniometer (Kernco Instruments Co. Inc., Texas). Drops of purified water (3 µl) were placed carefully on to surface of clean polymer film fixed to the glass slides through a syringe. Direct microscopic measurements of the contact angles were carried out on both sides of the drop within 3 min, assuming symmetry in the surface. The results were expressed as a mean of 12 measurements.

2.1.5 Determination of mechanical properties

Tensile properties of polymer sheet were determined as per ASTM D 412 using an Instron Automated Materials Testing system (IX) 1.09. The rectangular samples (7 cm × 0.5 cm) were tested with gauge length 25 mm and crosshead speed of 100 mm/min at room temperature. The ultimate strength, elongation percentage and elastic modulus (stress at 100% strain) were determined. The hardness was also determined with sheets of polymers piled to a thickness of 6 mm using a calibrated shore—A durometer as per ASTM D 2240. Dynamic mechanical properties of new polyurethanes were determined using a microprocessor controlled Rheovibron (DDV III C) instrument, Japan at amplitude of oscillation 0.1% under a dry nitrogen purge. Samples were cooled to $\approx$120°C and data were subsequently taken at a test frequency of 35 Hz and a heating rate of 1°C/min.

2.2 Studies on biomechanically induced biodegradation

2.2.1 Studies on stress-induced biodegradation

The poly(urethane urea) and poly(ether urethane urea)s were subjected to stress-induced mechanical degradation under physiological environment. An environmental stress cracking resistance test apparatus was used. The ASTM standard D 1695 was followed. The notched (controlled imperfection specimen (10 nos.) of uniform dimension were bent on to a copper holder and immersed in Ringer's solution and phosphate buffered saline (PBS) at 50°C for 2 days. The effect of bending stress and hydrolytic media (Ringer's solution and PBS) on the degradation was investigated. The proportion of the total number of specimens that crack in 48 h under higher temperature (>37°C) was observed.

2.2.2 Studies on strain-induced biodegradation

The poly(urethane urea) and poly(ether urethane urea)s were also subjected to strain-induced degradation. The rectangular coupons (5 × 0.5 cm) of the sample were subjected to 20% tensile strain and fixed tightly on glass rod using stainless steel wire. These strained samples were immersed in papain enzyme (2–8 units/mg solid, one unit will hydrolyze 1.0 mol) 10 mg and buffer medium for 30 days at 37°C. The activity of the enzyme was maintained by changing the enzyme medium by adding fresh enzyme (10 mg) in every 2 days interval. Then the samples were relieved of the strain, washed thoroughly with distilled water and dried at 60°C in vacuum oven. These aged and strained samples were subjected to tensile tests. An Instron Automated Materials Testing System (IX) 1.09 was used.

2.2.3 Studies on accelerated chemical degradation

The poly(urethane urea) and poly(ether urethane urea)s were subjected to accelerated degradation tests. Accelerated degradation tests were carried out using harsh chemical treatment mainly to predict the hydrolytic stability under the long-term use. The polymers were exposed in distilled water for 100 h and alcoholic potassium hydroxide (4%) solution for 4 h under boiling condition to determine the hydrolytic degradation. The change in dimension and weight was noticed.

3 Results

3.1 Synthesis of poly urethanes

The newly prepared poly(urethane urea)s HFL9-PUU, HFL13-PUU, HFL15-PUU and HFL18-PUU are ether free polymers. Since these polymers are prepared with chain-extender HDA, these polymers contain degradation-resistant urea linkages in hard segment and lesser percentages of urethane linkages in soft segments. Easily degradable ether or ester linkages were avoided and urethane linkages were minimised in the preparation of these novel poly(urethane urea)s. The poly(urethane urea) consists polyol component of HTPBD as soft segment as shown in

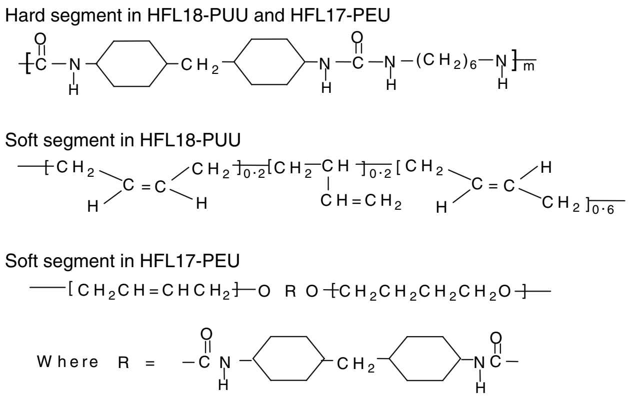


Fig. 1 Hard and soft segments of polyurethanes

Fig. 1. The mole ratio of hard and soft segment in poly(urethane urea), HFL18-PUU, is 75:25 (Table 1).

Poly(ether urethane urea)s HFL16-PEUand HFL17-PEU contain polyether polyol, PTMG and polyhydrocarbon polyol, HTPBD as soft segments combined through two urethane linkages. The soft segment-volume in the poly(ether urethane urea)s can be a regular array of either HTPBD or PTMG or alternate HTPBD and PTMG or irregular array of HTPBD and PTMG. Poly (ether urethane-urea), HFL17-PEU contains lesser degree of urea linkages in hard segment and higher degree of urethane and ether linkages in soft segment. The mole ratio of hard and soft segment in HFL17-PEU, is 68:32 (Table 1).

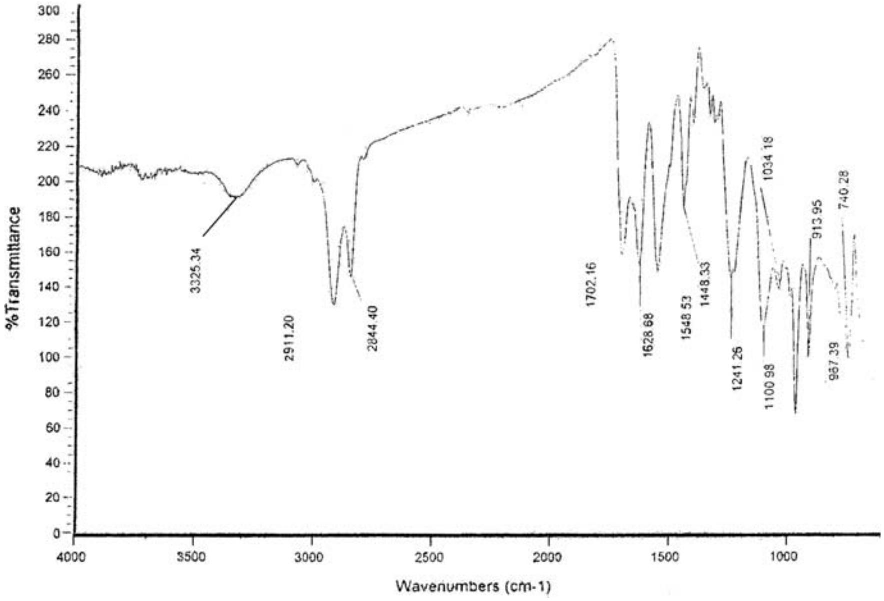
3.1.1 FT-IR spectral analysis

FT-IR analyses of present poly(ether urethane urea) HFL16-PEU exhibits an ether peak at 1,110 cm^{-1}. HFL16-PEU also shows peaks at 1,725, 1,702 and 1,631 cm^{-1} suggesting free urethane carbonyls, bonded urethane carbonyls and bonded urea carbonyls (ordered). FT-IR spectra of poly(ether urethane-urea) HFL17-PEU exhibit an ether peak at 1,101 cm^{-1}. It also showed peaks at 1,702 cm^{-1} for bonded urethane carbonyls and at 1,630 cm^{-1} for bonded urea carbonyls (ordered). FT-IR spectrum of poly(ether urethane-urea) HFL17-PEU is given in Fig. 2. FT-IR spectrum of poly(urethane urea) polymer, HFL18-PUU is given in Fig. 3. The absence of peak near 1,735 cm^{-1} gives absence of' amorphous region. The absence of peak for urea amide I at 1,660 cm^{-1} reveals the absence of non-hydrogen-bonded, free –N–H units of urea or free urea. The shift of urea peak towards lower wave number region is an indication of the extensive of hydrogen bonding between the urea carbonyl and the –N–H unit of another or the same polymer chains. The peak at 1,666 cm^{-1} for C=O stretching of urea carbonyl bonded (disordered) and urethane carbonyl around at 1,721 cm^{-1} are absent in the present poly(urethane urea)s.

3.1.2 Wide angle X-ray diffraction studies

The wide angle X-ray diffraction analyses (WAXD) data of poly(urethane urea)s also supports the formation of micro crystallites through virtual crosslinking. The WAXD curves for poly(urethane urea)s and poly(ether urethane urea)s are given in Fig. 4. The WAXD peak of poly(urethane urea) is more intense at 19° of 2θ angle scale corresponding to 4–5 Å *d*-spacing. Peak intensity at 19° of 2θ for WAXD spectrum of poly(urethane urea) is more than that of poly(ether urethane urea), even though they have same hard segment percentage. For example the

Fig. 2 Infrared spectrum of poly(ether urethane urea) HFL17-PEU



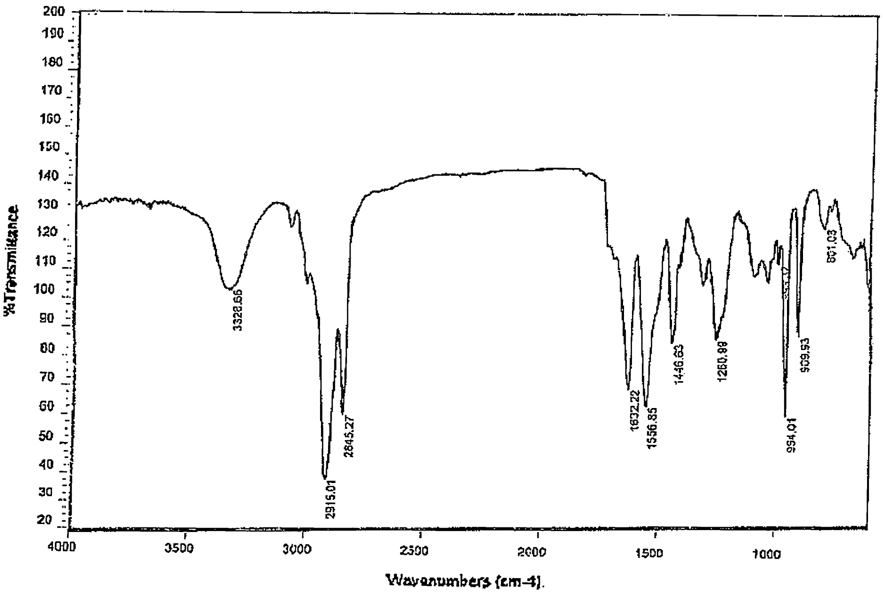


Fig. 3 Infrared spectrum of poly(urethane urea) HFL18-PUU

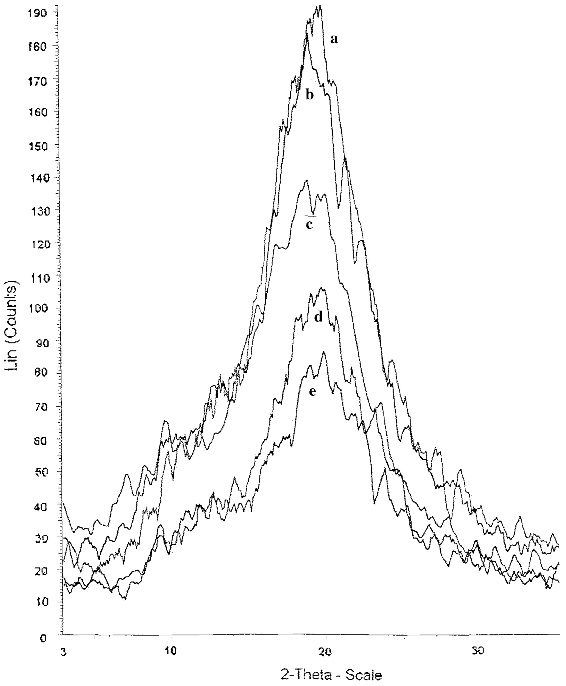


Fig. 4 Wide angle X-ray diffraction spectra of polymers. (**a**) HFL15-PUU, (**b**) HFL18-PUU, (**c**) HFL13-PUU, (**d**) HFL17-PEU, (**e**) HFL3-PU

WAXD peak of poly(urethane urea), HFL13-PUU is more intense than that of HFL17-PEU. Similar is the case of HFL9-PUU and HFL16-PEU. WAXD peak of poly(urethane urea) and poly(ether urethane urea) is more intense than that of poly urethane, HFL3-PU (prepared with methylene bis (*p*-cyclo hexyl isocyanate) $H_{12}MDI$, hydroxy terminated poly butadiene (HTPBD) and 1,4 butane diol). The WAXD peak of HFL18-PUU poly(urethane urea) is more intense at 19° of 2θ scale corresponding to 4–5 Å *d*-spacing than that in HFL16-PEU poly(ether urethane urea).

3.1.3 Studies on molecular weight between crosslinks

The physical crosslink density has been calculated based on swelling index and reported in Table 2. Higher crosslink density was observed for poly(urethane urea)s HFL13-PUU, HFL18-PUU and HFL15-PUU in comparison with other polymers. The addition of PTMG in HFL9-PUU (resulting HFL16-PEU) increases the crosslink density in HFL16-PEU. While the addition of PTMG in HFL13-PUU (resulting HFL17-PEU) reduces the crosslink density in HFL17-PEU.

3.1.4 Studies on contact angles

The data on contact angles are given in Table 3. Poly(urethane urea) HFL9-PUU (with polyol 42.5%) and poly(ether urethane urea) HFL16-PEU (with polyol 42.5%) have showed contact angles only 82.0° and 84.0°, respectively.

3.1.5 Studies on mechanical properties

The data on mechanical properties are given in Table 4. Tensile data of polymers reveal that all the polymers are of low elastic modulus. The tensile strength and elastic modulus increases with the increase of hard segment content (% chain extender). The ultimate strength increases

Table 2 Physical properties of polyurethanes

Polymer	Density (g/cm^3)	Swelling coefficient	Crosslink density ($\times 10^4$)	Molecular weight between crosslinks
Poly(urethane urea)				
HFL9-PUU	0.8916	4.1027	1.8520	5,399
HFL13-PUU	0.8905	2.5680	6.7810	1,475
HFL18-PUU	0.9483	2.2486	6.9460	1,440
HFL15-PUU	0.9555	1.9533	8.7375	1,144
Poly(ether urethane urea)				
HFL16-PEU	0.9552	4.2716	2.2600	4,427
HFL17-PEU	0.9174	3.6526	3.0900	3,238

Table 3 Surface properties of polymers

Polymer	Water contact angle (°)	Surface free energy	
		γ_{SV}	γ_{SL}
Poly(urethane urea)			
HFL9-PUU	82.0 ± 1.2	33.66	23.77
HFL13-PUU	83.0 ± 1.7	33.23	24.40
HFL18-PUU	85.4 ± 1.5	31.97	25.06
HFL15-PUU	85.0 ± 1.3	31.97	25.66
Poly(ether urethane urea)			
HFL16-PEU	84.0 ± 2.3	32.60	25.03
HFL17-PEU	83.2 ± 1.4	33.23	24.40

with increase in crosslink density. HFL15-PUU has the highest elastic modulus in comparison with all other polymers due to the higher crosslink density and higher hard segment content (80%). Moreover, the higher percentage of crosslinks in HFL15-PUU has resulted in reduced elongation (%) in comparison with that of all other polymers. HFL16-PEU and HFL17-PEU showed higher value of tensile strength compared to poly(urethane urea)s HFL9-PUU and HFL13-PUU of similar hard segment content. Poly(urethane urea), HFL18-PUU has elastic modulus 6.814 MPa. All the polymers have hardness in the shore A range, which was in agreement with the hardness of commercial polyurethanes of biomedical applications (e.g. Tecoflex (85A), Biomer (75A), Cardiothane (72A), Cadriomat (80A), Pellethane (80–90A), Elast-Eon (72–85A) etc.). The data on hardness of poly(urethane urea)s showed sharp increase in hardness with increase in the virtual crosslink density or hard segment content. Poly(ether urethane urea)s also showed a similar trend as discussed on tensile strength and crosslink density. The viscoelastic properties of the materials were determined from dynamic mechanical thermal analysis (DMTA). Dynamic storage modulus (E'), the dynamic loss modulus (E'') and the mechanical loss tangent (tan δ) are given in Table 5 and Fig. 5.

3.2 Studies on biomechanically induced biodegradation

3.2.1 *Studies on stress-induced degradation*

The data on the environmental stress corrosion-cracking test of the present polymers are given in Table 6. The poly(urethane urea)s and poly(ether urethane urea)s aged under environmental stress corrosion environment in Ringers solution and PBS media do not undergo any weight loss or ragged fracture. However, dimensional changes such as warping or hardening were observed with poly(ether urethane urea)s. These dimensional changes are due to the constantly applied bending stress. The polymer HFL18-PUU undergoes no weight loss and no visible change in stress-induced aging in Ringer's solution and PBS media. However HFL17-PEU becomes warped and hardened though there is no weight loss in Ringer's solution and PBS media.

Table 4 Mechanical properties of polyurethanes

Polymer	Ultimate tensile strength (MPa)	Ultimate elongation (%)	Elastic modulus (MPa)	Hardness shore A
Poly(urethane urea)				
HFL9-PUU	7.280 ± 0.600	336.0 ± 8.4	3.313 ± 0.240	71
HFL13-PUU	7.780 ± 0.678	207.4 ± 17.4	4.630 ± 0.161	73
HFL18-PUU	15.75 ± 0.600	336.9 ± 15.0	6.841 ± 0.267	80
HFL15-PUU	15.00 ± 1.09	151.3 ± 19.5	11.39 ± 0.435	90
Poly(ether urethane urea)				
HFL16-PEU	9.097 ± 1.527	335.5 ± 63.0	4.189 ± 0.049	75
HFL17-PEU	14.81 ± 1.10	273.4 ± 38.3	8.348 ± 0.519	80

Table 5 Dynamic mechanical properties of polyurethanes

Polymer	Glass transition temperature T_g (°C)	Storage modulus, E' (dyn/cm^2) ($\times 10^{-10}$)	Loss modulus, E'' (dyn/cm^2) ($\times 10^{-9}$)	Tan δ (E''/E')
Poly(urethane urea)				
HFL9-PUU	−66	88.9	3.11	0.35
HFL13-PUU	−67	1.06	3.49	0.33
HFL18-PUU	−66	1.18	4.00	0.39
HFL15-PUU	−65	1.25	4.24	0.40
Poly(ether urethane urea)				
HFL16-PEU	−72	56.8	2.21	0.39
HFL17-PEU	−66	1.31	2.49	0.20

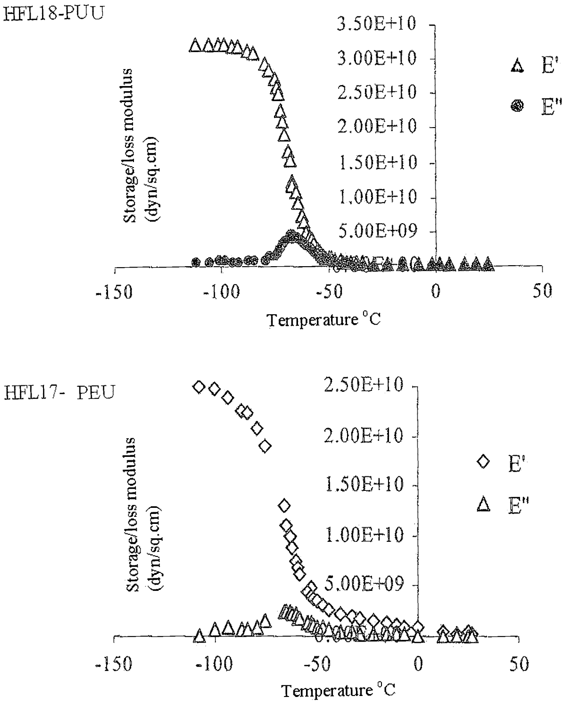


Fig. 5 Dynamic mechanical properties of HFL18-PUU and HFL17-PEU

Table 6 Stability of polyurethanes under stress-induced aging

Polymer	Nature of degradation	
	Ringer's solution	PBS
Poly(urethane urea)		
HFL9-PUU	Warped and harder	Brittle and warped
HFL13-PUU	Warped and harder	Brittle and warped
HFL18-PUU	No visible change	No visible change
HFL15-PUU	No visible change	No visible change
Poly(ether urethane urea)		
HFL16-PEU	Brittle and warped	Warped and harder
HFL17-PEU	Warped and harder	Warped and harder

3.2.2 Studies on strain-induced degradation

The studies on strain-induced degradation of the newly prepared poly(urethane urea), HFL18-PUU and poly(ether urethane urea), HFL17-PEU reveal interesting findings. The data of strain-induced biodegradation are given in Table 7. The polymers HFL18-PUU and HFL17-PEU aged in papain under strain and its buffer reveals increase of elastic modulus. Higher increase of elastic modulus is observed with HFL17-PEU aged in papain medium than in papain buffer. However increase of elastic modulus is observed with HFL18-PUU polymer aged in papain buffer than in papain enzyme. The FT-IR spectra of HFL18-PUU and HFL17-PEU aged under strained condition are given in Figs. 6 and 7, respectively. The spectrum of HFL18-PUU1 reveals appearance of strong peak at 1,705 cm^{-1} for bonded urethane carbonyl and 1,634 cm^{-1} for bonded urea carbonyl linkages. Similar spectral responses are also observed for HFL17-PEU.

4 Discussion

The hard segment in both poly(urethane urea) and poly(ether urethane urea)s, is comprised with urea linkages formed with diisocyante of H_{12}MDI and hexamethylene diamine (HDA) (Fig. 1). All the present polymers were prepared using mixture of solvents (dimethyl acetamide/toluene) having different solubility. Therefore, the premature phase separation of hard and soft segments occurs in the polymers due to the initial immiscibility of the reactants. However, the polyhydrocarbon based polyurethanes exhibit a high level of macro-phase separation when they are prepared in bulk and a high level of micro-phase separation when they are prepared in solution under homogeneous conditions. These effects are attributed to a large difference in their segmented structure and polarity. Moreover, polyurethanes based on hydroxy terminated polybutadiene do not favour hydrogen-bonding interaction

Table 7 Stability of polyurethanes under strain-induced aging

Polymer	Elastic modulus (MPa) and change of elastic modulus (%)			
	Buffer medium	% change	Papain enzyme	% change
Poly(urethane urea)				
HFL9-PUU	3.977	+20.0	4.075	+23.0
HFL13-PUU	5.469	+18.0	5.371	+16.1
HFL18-PUU	7.823	+14.3	7.792	+13.9
HFL15-PUU	12.88	+13.1	13.098	+15.0
Poly(ether urethane urea)				
HFL16-PEU	5.047	+20.5	5.718	+36.5
HFL17-PEU	10.719	+28.4	12.28	+47.1

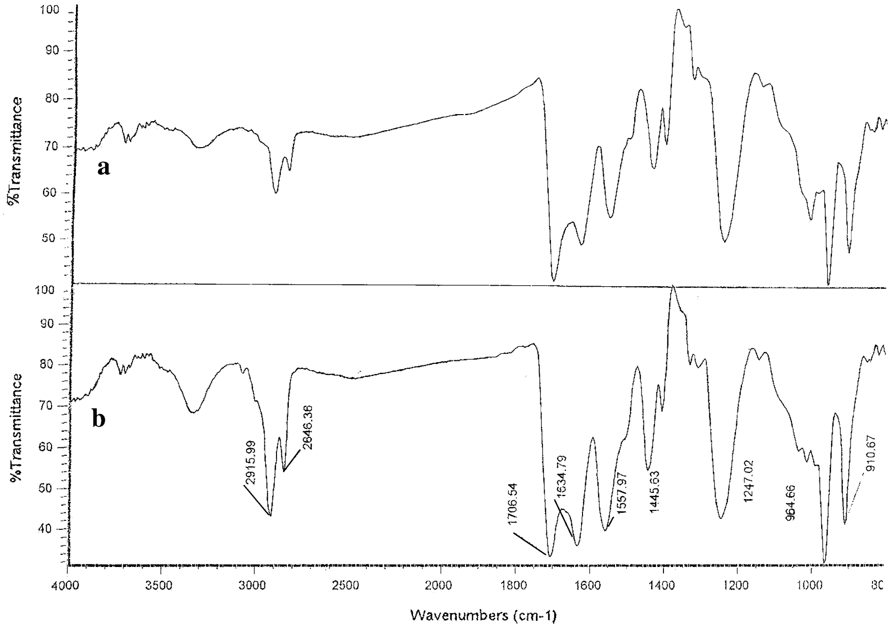


Fig. 6 FT-IR spectra of poly(urethane urea) HFL18-PUU aged under strain. (**a**) In papin enzyme, (**b**) in buffer control

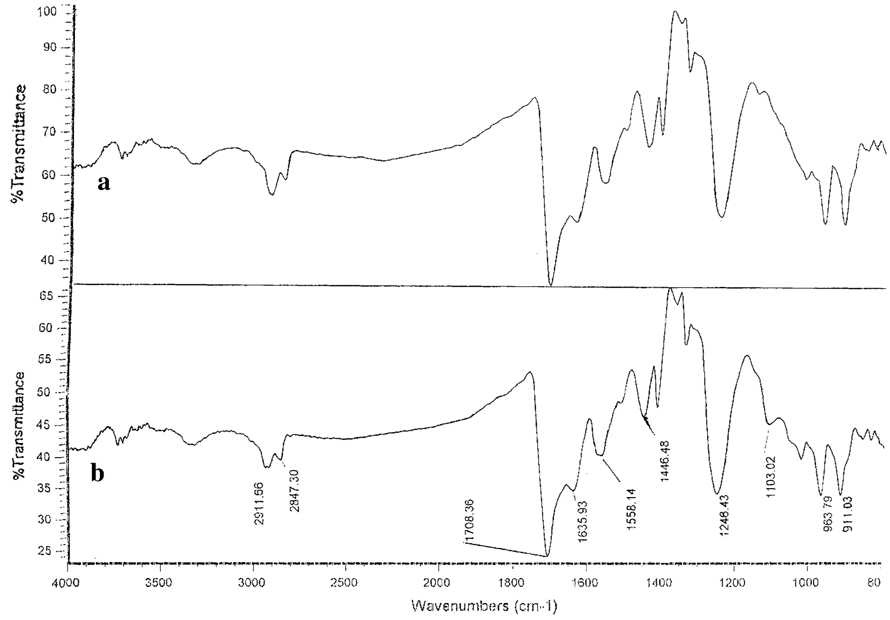


Fig. 7 FT-IR spectra of poly(ether urethane urea) HFL17-PEU aged under strain. (**a**) In papin enzyme, (**b**) in buffer control

between hard and soft segment units. As a result of this there exists, from thermodynamic point of view, a positive surface free energy and a positive heat of mixing. This serves as a driving force for the growth of phase-separated hard and soft segment domains. Hence the present polyhydrocarbon polyol (hydroxy terminated polybutadiene) based poly(urethane urea)s are more phase-separated than polyether polyol based poly(urethane urea)s and polyurethanes. In brief, all the present poly(urethane urea)s are considered to be segmented linear and microphase-separated polymers.

4.1 FT-IR spectral analysis

In poly(ether urethane urea)s, HFL16-PEU and HFL17-PEU in addition to the hydrogen bonding interaction (virtual crosslinking) through urea–urea and urethane–urea there are two more types of hydrogen bonding interaction through ether–urea and ether–urethane. However, the crosslinks of these types provide phase mixing between the hard and soft segments, as ether group in poly(ether urethane urea)s is present in the soft segment region. The addition of PTMG leads to the hydrogen bonding of ether units of PTMG with urethane or urea groups of hard segment and phase mixing due to hydrogen bonding between soft-segment and hard-segmented urea. However, the phase mixing in HFL16-PEU and HFL17-PEU could be moderately due to presence of hydrophobic polyols.

The strong bonded urea and urethane carbonyl peak in the spectrum of poly(urethane urea), which does not contain polyether segment, clearly shows hydrogen bonding interaction of urethane–urea and urea–urea groups. In poly(urethane urea) HFL9-PUU, HFL-13PU, HFL15-PUU and HFL18-PUU, only urethane–urea interactions may lead to phase mixing. Since the concentration of urethane linkage is very low, the chances of phase mixing are minimal. The urea linkages are involved in excessive three-dimensional hydrogen bonding leading to long-range ordering and crosslinked state as reported elsewhere [13]. The three-dimensional network in hard segments appears as hard domains.

The absence of the peak at 1,666 cm^{-1} for C=O stretching of urea carbonyl bonded (disordered) and urethane carbonyl around at 1,721 cm^{-1} in the present poly(urethane urea)s confirmed the formation of short- and long-range ordering of urea hydrogen bonding which reflects the formation of crystallites in hard domains. The IR analyses revealed the formation of short- and long-range ordering of urea hydrogen bonding leading to the formation of crystallites in hard domains.

All the poly(urethane urea)s are linear polymers. None of the polymers has showed peaks for allophanate linkages responsible for true covalent crosslinking. Allophanates are formed due to reaction between free isocyanates and polyurethane prepolymer, if isocyanate index is high. Allophanate linkages are normally characterized by a triplet of intense band in IR centered at 1,220, 1,280 and 1,310 cm^{-1} associated with skeletal vibrations of allophanate group as well as unique N–H bands at 3,298, 3,267 and 3,233 cm^{-1} [14]. The absence of these bands in the IR spectra of the poly(urethane urea)s demonstrated that undesirable side reactions had not occurred. Further more the absence of the band at 2,270 cm^{-1} suggested that free isocyanates were not physisorbed to the polymer as un reacted form and the absence of free isocyanate end groups.

4.2 Wide angle X-ray diffraction studies

The more intense WAXD peak at 19° observed in poly(urethane urea)s especially with HFL18-PUU than that in poly(ether urethane urea) especially with HFL16-PEU; this is attributed to the presence of microcrystallites by short-range ordering in hard segment domains mediated by urea–urea hydrogen bonding interactions. A similar observation has been observed by earlier investigators in the case of poly(ether urethane urea)s based on toluene diisocyanate, PTMG, poly(butylene adipate) and ethylene diamine [15].

The present study reveals the presence of micro crystallite formation in poly(urethane urea)s in hard segments in spite of the isomeric forms of the H_{12}MDI due to extensive hydrogen bonding interactions, which were hitherto observed only in aromatic poly(urethane urea)s. Formation of similar crystallites has been noticed only in aromatic poly(urethane ureas) such as Biomer® based on MDI. No studies on the crystallites formation in aliphatic poly(urethane urea) have been reported so far. The present studies reveal the formation of crystallites in aliphatic poly(urethane urea)s based on H_{12}MDI.

Though HFL17-PEU contain crystallizable PTMG soft segment, there was no individual intense crystallite peak for the crystallizable PTMG soft segment (Fig. 4). The absence of intense crystallite peak was due to the lack of greater phase-separation in HFL17-PEU. Owing to the smaller molecular weight of PTMG and the presence of ether group in the soft segments, phase mixing with hard segments thorough urethane–urea and ether–urea hydrogen bonds may be more predominant in HFL17-PEU.

4.3 Studies on molecular weight between crosslinks

The physical crosslink density is defined as the degree of secondary level molecular interactions, particularly hydrogen bonding, between the various electrically charged linkages present along the polymer chain of poly(urethane urea)s. The virtual crosslinking in poly(urethane urea)s, HFL9-PUU, HFL13-PUU, HFL18-PUU and HFL15-PUU are through hydrogen bonds between urethane–urea, urea–urea and urethane–urethane linkages. The extensive hydrogen bonding interactions in poly(urethane urea)s resulted to a thermosetting-like character. The bond strength of physical crosslinks are approximately 1/20th of true covalent bond strength, and may be formed, broken and reformed on infinite number of times in a highly flexing environment. High degree of physical crosslinking enables the polymer to attain high flex life.

The higher crosslink density can enable improved biodurability. The increased crosslink density observed in HFL15-PUU and HFL18-PUU is due to increased urea–urea hydrogen bonding because of the higher percentage of hard segment content. In general higher the concentration of amine chain extender in a particular series of poly(urethane urea)s higher the virtual crosslink density. As the percentage of amine content increases in poly(urethane urea)s, the sites of hydrogen bonding (urea linkage) increases and virtual crosslink density increases. This is because urea or diamide group has C=O bond flanked by two N–H groups. The oxygen atom of the C=O group of one hard segment part can effectively undergo hydrogen bonding with hydrogen atoms of the N–H groups of second hard segment part and so on. This will lead to short- and long-range of secondary interactions leading to microcrystallites formation in poly(urethane urea)s.

The crosslink density of HFL9-PUU and HFL13-PUU reveal appreciable difference. The chemical composition and crosslink density of two poly(urethane urea)s indicate the transition from highly elastomeric nature in the former to the reduced elastomeric nature in the latter. Addition of PTMG polyol in these poly(urethane urea)s alter the crosslink density differently.

The crosslink density of HFL17-PEU was lower when compared with HFL18-PUU which is attributed to the phase mixing and disruption of three-dimensional net works to some extent in the former. However both these polymers were found to be insoluble in known organic solvents such as dimethyl acctamide, dimethyl formamide and terahydrofuran. The crosslink density and molecular weight between crosslinks reveals high degree of virtual crosslinking resembling a thermosetting like character in these polymers.

4.4 Studies on contact angles

The measurement of contact angles in an aqueous environment is particularly useful for biomedical materials, as they are employed in an environment that is predominantly water. Water contact angle is an indicator of the wettability of surface. The data on contact angles are given in Table 3. Both poly(urethane urea) HFL9-PUU and poly(ether urethane urea) HFL16-PEU containing polyol 42.5%, have showed contact angles only 82.0° and 84.0°, respectively. Hence it can be inferred that the introduction of more urea linkages in the present poly(ether urethane urea)s and poly(urethane urea)s could alter the hydrophobic–hydrophilic balance.

However, all these polymers are categorized as hydrophobic. Since contact angle studies were conducted in air medium it could be inferred that hydrocarbon polyol is present at the air-surface. The hydrophobicity of the present polymers is a favorable factor for blood contact applications of polymers as it can enhance albumin adsorption and reduce platelet adhesion on the surface of these polymers.

4.5 Studies on mechanical properties

Tensile studies of the present polymers reveal that all the polymers have low elastic modulus. Polyurethanes used as vital components in biomechanically sensitive blood contact devices such as pump membrane of blood pumps and flexible leaflet of artificial hearts and left ventricular assist devices should have low elastic modulus which can allow repeated cyclic flexing in biological conditions. Moreover, low elastic modulus polyurethanes with reduced bending stress can allow the membrane to flex more freely without producing adverse changes in blood flow. The required range of elastic modulus of polymers for use in cardiac assist devices such as trileaflet heart valve is 5–8 MPa. Accordingly, poly(urethane urea), HFL18-PUU having elastic modulus 6.814 MPa is a suitable material for application in cardiac assist devices. Commercial polyurethane viz. Elast-Eon® also possesses low elastic modulus of 5–10 MPa. The increased tensile strength observed in HFL16-PEU and HFL17-PEU in comparison with that of HFL9-PUU and HFL13-PUU is due to the strong phase mixing interaction offered by the ether–urea and ether–urethane linkages.

The mechanical properties such as tensile strength, elongation (%), elastic modulus and hardness are influenced by many parameters such as molecular weight of the polyol, hard to soft segment ratio, crystallite formation and virtual crosslinking. Generally as the hard segment content increases the virtual crosslink density increases and formation of microcrystallites also increases. It is observed that with the increase of virtual crosslink density, the tensile strength and elastic modulus increases while the elongation (%) decreases. This may be attributed to the increased hard segment aggregation due to urea–urea interactions and also due to the increase in hard segment percentage or amine content.

DMTA provides information on first- and second-order transitions (T_m and T_g), the degree of phase separation, crystallinity and crosslinking of polymer and the mechanical properties such as the glassy state and the rubbery plateau modulus. For materials, which have a higher value of loss tangent, energy used to deform the material is dissipated as heat and to cause changes in the polymeric structure by movements of polymeric segments or atomic grouping. Clinically the damping that results from a higher value of loss tangent is likely to produce a degree of stress relief under functional forces. The loss modulus of HFL18-PUU is appreciably high to produce higher degree of stress relief under functional forces. Therefore HFL18-PUU polymer shall have a sufficient cushioning effect to distribute and absorb functional stress and remain stable over time indented for long-term performance in biomechanically flexing environments.

4.6 Studies on biomechanically induced biodegradation

4.6.1 Studies on stress-induced degradation

Biodegradation of segmented polyurethanes has been considered as the failure of polyurethane due to combined effect of stress and physiological fluids. A state of stress either externally applied or processing-induced is a dominant factor in environmental stress cracking (ESC) of polyurethane biomaterials. The reported failure of poly(ether urethane) insulated cardiac pacemaker leads is attributed to environmental stress corrosion cracking (ESC). Stress may be inherent due to the phase separated nature of polyurethanes or may be applied to a device during manufacture, implantation, or through intracorporeal movement.

Environmental stress cracking is characterized by deep, ragged fracture or surface pitting within polyurethane often occurring perpendicular the direction of stress. No weight loss and visible dimensional change has been observed in HFL18-PUU during stress-induced aging in Ringer's solution and PBS media. Warping and hardening observed in HFL17-PEU is attributed to realignment of polymer chain along the direction of stress leading to increased hardness. This trend is more possible in the presence of PTMG soft segment. The absence of weight loss in HFL17-PEU indicates no breaking of chemical bonds. However the change in shape of aged HFL17-PEU sample is not a reversible one.

4.6.2 Studies on strain-induced degradation

Papain is a thiol endopeptidase enzyme, which exhibits a similar enzymatic activity of lysosomal enzymes. Papain has specificity to peptide bond degradation. Urethane (–NH–CO–O–) or urea (–NH–CO–NH–, diamide) linkage in poly(urethane ureas) is more or less similar to that of peptide (–NH–CO–, amide) in protein, studies based on papain-induced hydrolytic degradation is more appropriate. Takahara et al. [16] has showed more degradation in vitro of hydrophilic poly(ethylene oxide)-based polyurethane in the presence papain. Angeline et al. [17] (1990) have reported long-term enzymatic degradation of Pellethane in papain under in vitro and reported significant reduction in tensile strength and molecular weight.

Hydrophobic polyol, hydroxy terminated polybutadiene (HTPBD) is a versatile polyol that polyurethanes based on which have been widely used as high performance composite propellants for space applications [18]. But the application of HTPBD in biomedical uses for the fabrication of long-term devices is limited. This is due to reported poor biostability of polyurethane containing HTPBD [19]. The polyurethanes prepared from hydrogenated polybutadiene, hydroxy terminated polybutadiene and poly(dimethyl siloxane) exhibited weight loss due to aging in papain solution [16]. It has been reported that, Biomer^{R}, a poly (ether urethane urea) undergoes degradation in vitro in papain solution [20–23]. FT-IR-ATR studies have indicated the formation of primary aromatic amines due to hydrolytic degradation of Biomer aged in papain solution [24].

Generally, enzymes and other swelling agents can effectively plasticize the polymer materials and reduce the modulus, tensile strength and elongation by affecting the phase-separated structure [25]; the strain-induced polymers HFL18-PUU and HFL17-PEU aged in papain and its buffer reveals increase of elastic modulus. The applied strain on the polymer in buffer medium is also found to influence the elastic modulus. Higher increase of elastic modulus observed with HFL17-PEU aged in papain medium than in papain buffer is due to the combined effect of papain enzyme and induced-strain. However increase of elastic modulus observed with HFL18-PUU polymer aged in papain buffer than in papain enzyme is possibly due to insignificant effect of papain enzyme with HFL18-PUU polymer. The elastic modulus of strained HFL18-PUU sample is 8.934 MPa in papain enzyme, which is slightly above the required limit of 5–8 MPa. In the present aliphatic poly(urethane urea)s, the strained polymer undergoes unidirectional reorganisation of polymer chains leading to increase of elastic modulus significantly. Similar studies by Fare et al. using Corethane (polycarbonate urethanes based on MDI/poly(1,6-hexyl-1,2-

ethylcarbonate/BD) and Coremer (polycarbonate urethane urea based on MDI/poly(1,6-hexyl-1,2-ethylcarbonate/ED) reveal that increased rearrangements of hydrogen bonds between the carbonate and urethane/urea groups that took place under constant mechanical strain during the aging [26]. However, under repeated flexing environment of actual clinical situation, the possibility of formation of unidirectional reorganisation of polymer chains is negligible. Moreover the increase in elastic modulus observed could be reversed under a continuously flexing environment as hydrogen bonds can form and break repeatedly.

FT-IR studies of the strained and aged sample HFL18-PUU revealed the absence of degradation at the urethane or urea linkages and degradation products like primary amine, butyric acid or succinic acid as reported elsewhere [26]. The in vitro aging studies in papain enzyme and its buffer control reveal that the effect of hydrolytic enzyme papain on the hydrolytic degradation of the present polymer, HFL18-PUU is not very significant. This is due to the absence of substrate site-specific interaction of the enzyme, since the surface of the polyurethanes is more hydrophobic. Moreover, the virtually crosslinked urea groups in hard segment of the poly(urethane ureas) are more resistant to the hydrolysis as suggested by Takahara [16].

Previous studies have shown that both polyester and polyether based poly(urethane urea)s are susceptible to cleavage by hydrolytic enzymes. It was also shown that the degree of hard segment micro-domain formation in polyurethane materials as well as its structure influences the ability of enzymes to degrade the polymers. Santerre and Labow have formulated a relation ship between the formation of hard segment domain and the hydrolysis of urea/urethane grouped in poly(ether urethane urea)s [27]. They showed that the polymer containing the highest number of urea and urethane bonds exhibited the least degradation. The present poly(urethane urea), HFL18-PUU having 75% of hard segment favours hard segment micro-domain and creates protective structure for the hydrolysable hard segment linkages located within the micro domains as reported elsewhere [27]. It is hypothesized that the virtual crosslinking in present poly(urethane urea), HFL18-PUU facilitate the formation of protective micro domain phase separated-structure in poly(urethane urea). The present studies indicate that the HFL18-PUU1 and HFL17-PU2 could be resistant to strain-induced degradation.

4.7 Accelerated chemical degradation

The studies with accelerated aging in highly severe experimental conditions (boiling water for 100 h and boiling alcoholic potassium hydroxide for 4 h) is important for the prediction of long-term performance in short-term. Fare et al. 1999 has used medium like concentrated nitric acid or alkaline sodium hypochlorite to evaluate degradation of polyurethanes even though such severe conditions cannot be found in the human body [26]. Ismail et al. have also studied the hydrolytic stability of polyurethanes elastomers by boiling the weighed specimens under reflux for 24 h in deionised water, 2 M hydrochloric acid and 2 M sodium hydroxide solution [28].

The polymer HFL17-PEU exposed in boiling water for 100 h does not reveal significant change in weight. But HFL17-PEU exposed in boiling alcoholic potassium hydroxide undergoes degradation and fragmentation with significant weight loss. However the polymer HFL18-PUU is stable in both these accelerated chemical degradation. The accelerated test in harsh and aggressive chemical conditions clearly indicates that poly(urethane urea), HFL18-PUU would excellently stable in physiological condition.

The present poly(urethane urea) polymers based on H_{12}MDI-HTPBD-HDA are unique because no aliphatic and physically crosslinked poly(urethane urea) has been developed from H_{12}MDI and HTPBD thus far. The poly(urethane ureas) reported thus far are made from aromatic diisocyanate, MDI with polyether polyol, or hydrogenated/hydroxy terminated polybutadiene.

5 Conclusion

The biomechanical studies on poly(urethane ureas) reveal remarkable biomechanical stability in the case of poly(urethane urea) (HFL18-PUU). The aging under induced-stress (environmental stress corrosion cracking) (ESC) in Ringer's solution and phosphate buffered saline reveals resistance in the case of poly(urethane urea) (HFL18-PUU). The aging under induced-strain (20% tensile strain) in hydrolytic enzyme medium, papain and in buffer also reveals resistance in the case of poly(urethane urea) (HFL18-PUU). The studies on accelerated chemical degradation reveal no degradation in the case of poly(urethane urea) (HFL18-PUU). The superior performance of the newly developed poly(urethane urea) (HFL18-PUU) is attributed to the virtually crosslinked structure present in hard segment domain.

The in vitro cytotoxicity studies of these polymers by direct contact and with the extract of the polymers reveal that all the polymers are non-cytotoxic. The studies on blood-material interaction reveal that the platelet consumption in whole blood in the presence of novel poly(urethane urea) polymers is minimal which is attributed to the three-dimensional virtual crosslinking and microphase separated hard segment domain morphology [10–12]. Poly(urethane urea), HFL18-PUU synthesised with aliphatic diisocyanate dicyclohexyl methane diisocyanate, hydroxy terminated polybutadiene and hexa methylene diamine is a promising candidate elastomer for long-term blood contact applications such as heart valve and blood pump.

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