Controlled Release of Model Drug from Biodegradable Segmented Polyurethane Ureas: Morphological and Structural Features

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Summary: Segmented polyurethane ureas (SPUUs), which are being used in implant devices, were evaluated as drug delivery matrices using theophylline as a model drug without much sacrificing the mechanical properties of films after drug doping. SPUUs were synthesized from aliphatic diisocyanate (lysine methyl ester diisocyante (LDI)), poly(caprolactone) diol with molecular weights 530, 1250 and 2000 and 1,4-butanediamine. Three series of segmented SPUUs were prepared with various soft segment lengths and were characterized by Fourier transform infrared spectroscopy, dynamic viscoelastic measurements and tensile testing. A single tanδ peak was observed in dynamic viscoelastic measurements, which revealed phase mixing of hard and soft segments. Low elongation at break was observed in case of PCL 2000 based SPUUs, may be due to partial cystallization of PCL segment. The degradation of SPUUs in alkaline solution and *in vitro* drug release of theophylline in pH 7.4 buffer were also investigated. The drug release behavior from these films were analyzed by the exponent relation $M_t/M_\infty = kt^n$, where k and n are constants and M_t/M_∞ is the fraction of drug released until time, t. The constant n was found to be close to 0.5 in all samples, which suggests the release of drug from these polymers can be explained by the Fickian diffusion model.

Keywords: *in vitro* drug release; lysine-based diisocyanate; mechanical properties; morphology; segmented polyurethane ureas

Introduction

Many biomedical devices, such as catheters, blood pumps, prosthetic heart valves and insulation for pacemakers, are made from polyurethanes.[1,2] A promising approach for the development of new controlled-releasing preparations is use of polyurethane materials as the basis of drug delivery systems. Polyurethanes have the broadest application because they can be designed in any desired forms as well as degrading satisfactorily in the human body and being eliminated from it. Thus, polyurethanes are an important class of polymers that have found many applications as biomaterials on account of their excellent physical properties and relatively good biocompatibility.[3] The design of the polyurethane controlled-release forms for therapeutic drug administration is the subject of intense interest. The polyurethane carrier is utilized to deliver iodine-containing drugs.[4] Urethane-based hydrogels have been prepared based on the reaction of diisocyanates with amphiphilic ethylene oxide and triol crosslinker to deliver propranolol hydrochloride, an antihypertensive drug.[5] An adhesive skin-containing layer on the base of the polyurethanes is designed to administer nicotine to help people stop smoking.[6] It has been reported that monolithic devices of segmented polyurethanes to regulate both release rate and transport mode of drug release have

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been developed.[7] Chaudhuri *et al*.[8] incorporated the nucleoside isopentyladenosine into a polyurethane delivery system. Results from this study demonstrated that effective *in vitro* antileukemic activity was obtained by the prepared polyurethane system.

Methylene bisphenyl diisocyante (MDI) and toluene diisocyante (TDI) are the most popular diisocyante components in polyurethane. However, MDI and TDI based polyurethanes yield toxic aromatic diamines upon degradation. Development of diisocyanates based on lysine has removed this obstacle. Physical, structural characterisation and degradation behaviour of segmented polyurethanes, obtained from lysine based diisocyanate have been recently reported.[9] The purpose of this study is to prepare three segmented polyurethane ureas by using lysine diisocyanate, polycaprolactone diol of three different molecular weights (Number average molecular weight M_n, 530, 1250, 2000) and 1,4-butanediamine (BDA) as chain extender and thus obtained SPUUs have been characterized by suitable analytical techniques. We have also investigated the feasibility of controlling the release rate of a model drug from these polymers.

Experimental

Materials

2,6-diisocyanato methyl caproate (LDI, Kyowa Hakko Co., Ltd.), polycaprolactone diol with M_n of 530, 1250 and 2000 (PCL, Aldrich Chemical), and 1,4-butanediamine (BDA, Aldrich Chemical) were used for the synthesis of SPUU. LDI, BDA and dimethyl formamide (DMF, Nacalai Tesque, Co., Ltd) were purified by vaccum distillation. PCL was placed in a vaccum oven at 353 K over 24 h to remove residual water before reaction. Theophylline, phosphate buffer saline (PBS) (pH = 7.4) (Aldrich chemical) were used directly as received.

Synthesis of Segmented Polyurethane Ureas (SPUUs)

SPUUs were synthesized via a standard two step prepolymer method[10, 11] using LDI, PCL diol (M_n 530, 1250 and 2000) and BDA as a chain extender. Briefly, PCL was placed in a 4-necked kettle equipped with a mechanical stirrer, a thermometer, and N_2 bubbler and heated to 358 K then LDI was added slowly to the kettle. The molar ratio of polyol to diisocyanate was 1:2. The reaction proceeded at 358 K for 3 hrs in the N_2 flow. The reaction mixture was cooled to room temperature and anhydrous DMF (to make the reactant concentration approximately 20% (w/v)) was added and stirred for 15 minutes. Then the chain extender in DMF solution was added at a 1:1 molar ratio with the prepolymer and allowed to react for approximately 10 hrs. The polymer was precipitated in excess distilled water and vacuum filtered. The polymer was then dried under vacuum at 333 K for 24 hrs, stored in a desiccator until use.

The composition and sample code of SPUUs were summarized in Table 1. Sample code was designated as PCL(PCL M_n)(PCL fraction)BDA. All solid films were prepared by solution casting. The SPUUs were dissolved in DMF at a concentration of 10% w/v, the polymer films cast for the degradation, tensile and dynamic mechanical

Table 1.
Characterization of segmented poly (urethaneureas).

Sample code	Molar ratio LDI: PCL: BDA	M_w	M_n	M_w/M_n	PCL fraction*
PCL(530)(50)BDA	2: 1: 1	206000	61400	3.3	50
PCL(1250)(70)BDA	2: 1: 1	121000	44500	2.7	70
PCL(2000)(80)BDA	2: 1: 1	36500	17000	2.1	80

* PCL fraction has been calculated based on the total weight of the composition used.

testing were obtained by pouring the polymer solution (15 ml) into a 8 cm diameter PTFE petri dish (casting dish). The dishes were covered to prevent the film from contamination of dust and excessively fast evaporating the solvent. The cast films were dried under vacuum at 333 K for 48h to remove residual solvent.

Characterization

SPUU films were characterized by dynamic viscoelastic measurement, Fourier transform infrared (FT-IR) spectroscopy, and tensile tests.

in vitro Degradation

Degradation studies were performed by exposing the polymer films to an alkali solution. Hydrolysis tests were carried out by using 1N NaOH solution. Each SPUU film (disc-shaped 0.3 mm thickness) was placed into individual vial containing 10 ml of 1N NaOH solution and incubated at 310 K. The films were observed from time to time and total time taken for complete digestion of films into soluble materials was determined. Each degradation experiment was repeated three times ($n = 3$).

Theophylline Loading

1, 3 and 5 wt% of drug, with respect to polymer sample, was dispersed in the DMF solution for 2 hrs. After complete dispersion/dissolution of drug, the homogeneous solutions were poured into a PTFE casting dishes. The cast films were dried under vacuum at 333 K for 48h to remove residual solvent and films were released from casting dishes and then trimmed to 10 mm $\times$ 10 mm and resulting films were used for *in vitro* drug release studies. Nine formulations of the films were prepared out of three polymers. These polymers were designated as PCL(530)(50)BDA-TP1, PCL(530)-(50)BDA-TP3, PCL(530)(50)BDA-TP5, PCL(1250)(70)BDA-TP1,PCL(1250)-(70)-BDA-TP3, PCL(1250)(70)BDA-TP5, PCL(2000)(80)BDA-TP1, PCL(2000)-(80)BDA-TP3 and PCL(2000)(80)BDA-TP5. TP1, TP3 and TP5 are the 1, 3 and 5 wt% of theophylline drug in the respective SPUU films.

in vitro Drug Release Studies

In order to record the release behavior of theophylline, known weights of drug containing SPUU films (about 0.05g) of 0.3 ± 0.02 mm thickness and 10 mm $\times$ 10 mm square shaped samples were placed in vials containing 20 ml of phosphate buffer saline (PBS) (pH 7.4) and placed in a shaking water bath at 310 K at 100 rpm. Aliquots (0.5 ml) were withdrawn periodically to determine drug concentration and, in all cases, equal volumes of dissolution medium were immediately added to maintain a constant volume. Theophylline concentration was determined spectrophotometrically at 274 nm. Absorbance from blank (SPUU films without drug) as a function of time was systematically measured and subtracted from the drug loaded films absorbance value. This measurement ensured to take into account of any unreacted material that leached in to external solvent that might occur during the time of release experiments. Samples were withdrawn until two successive aliquots showed no increase in absorbance. The amount of theophylline released from the SPUU films in a dissolution medium, at a given time, was calculated using standard curve of theophylline in corresponding buffer and expressed as percentage of total drug content of the investigated films. Experiments were performed in triplicate, and the average value was considered while data treatment and plotting.

Results and Discussion

Characterization

SPUUs were synthesized by a two-step polymerization method.[10, 11] Polycaprolactone (PCL) diols were first reacted with two equivalents of the diisocyante. Subsequent chain extension was arrived by reaction with an equivalent amount of a diamine. The final polymers were purified properly by reprecipitation, vacuum dried and then analyzed. The characteristics of SPUUs are listed in Table 1. The molecular weights were determined by GPC. Since a

peak position calibration curve based on polystyrene standards was used to calculate molecular weights, the values obtained are only relative magnitude. All the SPUUs obtained appear as white products.

Fig. 1 shows the FTIR spectra of SPUUs, two main spectra regions are important in this study: carbonyl stretching vibration at 1600 to 1800 cm^{-1} as well as the NH stretching vibration at 3200 to 3550 cm^{-1}. For the PCL polyurethanes, the carbonyl stretching region (1650 to 1800 cm^{-1}) is dominated by the intense soft segment ester band which is located at 1730 cm^{-1}. The potential hydrogen bonding acceptors are the urethane/urea carbonyl oxygen of the hard segments and the ester carbonyl in the soft segments. Free carbonyl groups give signals at 1740 cm^{-1}, where carbonyls involved in hydrogen bonding are known to appear at 1730 cm^{-1}. As can be seen in Figure 1 the decrease of PCL M_n results in an increase in the intensity of the absorption band at 1552 cm^{-1} and a decrease in the intensity of the band at 1168 cm^{-1}. These are indicative of a higher concentration of urethane/urea groups and a lower concentration of ester groups, that is, a higher content of hard segments in polyurethane ureas. In the amine region, a broad peak centered at around 3335cm^{-1}, corresponding to N-H stretching in hydrogen bonded urea groups[12] grows with the increase in urea group concentration that takes place with the decrease on the PCL length or decrease in PCL fraction in SPUUs (see Table 1), as expected. We do not see any evidence of free (non-hydrogen bonded) N-H groups (vibrations to be found at approximately 3450 cm^{-1})[13]. Thus, urethane urea formation has been confirmed from IR analysis.

Tensile Tests

Stress-strain curves of PCL(530)(50)BDA and PCL(1250)(70)BDA films with and without drug loaded are illustrated in Figure 2. Characteristic values derived from these curves are presented in Table 2.

All curves are shown upto the fracture stress point of the samples. Clearly three different regimes are visible. First, the behaviour at low deformations can be explained as the pure elastic deformation belonging to normal elastomers.[14] Secondly, the area of plastic deformation at strains between 200 to 600. This is almost the same for both the polymers (with and without drug loaded), may be due to shear induced crystal fragmentation. Thirdly, at strains above 600% an upswing can be observed, which can be attributed to strain

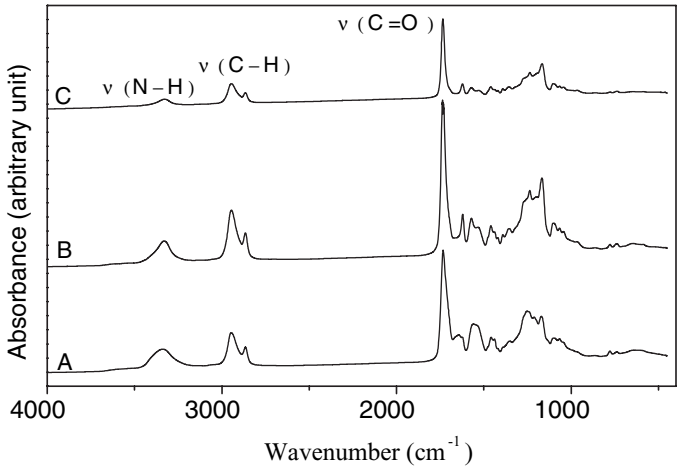

Figure 1.
FTIR spectra of SPUUs, A) PCL(530)(50)BDA, B) PCL(1250)(70)BDA, C) PCL(2000)(80)BDA.

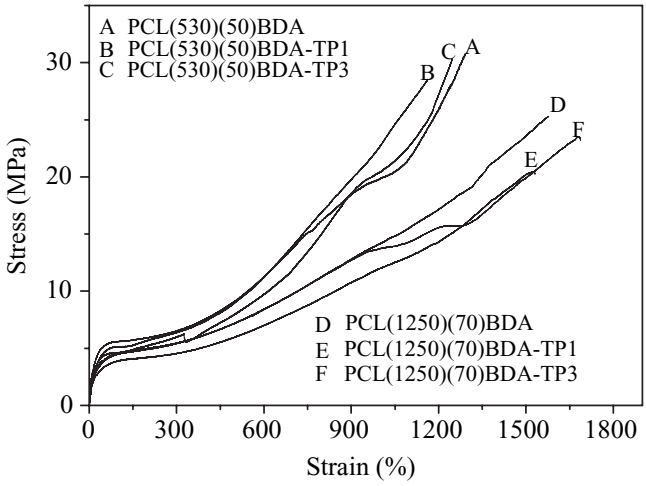

Figure 2.
Uniaxial stress-strain curves of with and without drug loaded SPUU films with two different PCL molecular weights.

induced crystallization of soft segment chains. Similar results were found in case of PCL-based polyurethanes.[15]

The trend of increasing tensile properties with increasing hard segment content could be attributed as the hard segment may act as a reinforcing filler or physical crosslinker to the total polymer network. It could also be explained that increasing PCL molecular weight leads to decreasing polyurethane urea molecular weight (Table 1) and this may be expected to result in decreasing tensile properties, as observed. The low tensile and elongation at break for PCL(2000)(80)BDA can be attributed to the low M_n and partial crystallization of PCL. There were no readily interpretable effects of varying the PCL segment length on mechanical properties, and no obvious effect of polydispersity index, although both parameters might be expected to play a role.

Dynamic Viscoelastic Measurements

For the SPUUs synthesized, an increase in soft segment length automatically leads to decrease in hard segment content and increase in soft segment content. The soft segment contents in PCL(530)(50)BDA, PCL(1250)(70)BDA and PCL(2000)(80)-BDA are about 50, 70 and 80%, respectively. Figure 3 shows the temperature dependencies of dynamic storage modulus (E′) and loss modulus (E″). The

Table 2.
Tensile properties of SPUUs (±SD, n = 4)

Sample code	Tensile Strength (MPa)	Strain at break (%)
PCL(530)(50)BDA	30.7 ± 1.7	1290 ± 10
PCL(530)(50)BDA-TP1	28.5 ± 1.4	1162 ± 10
PCL(530)(50)BDA-TP3	30.2 ± 1.8	1250 ± 10
PCL(1250)(70)BDA	25.3 ± 1.2	1580 ± 10
PCL(1250)(70)BDA-TP1	23.2 ± 2.4	1490 ± 10
PCL(1250)(70)BDA-TP3	24.6 ± 1.8	1600 ± 20
PCL(2000)(80)BDA	10.0 ± 2.5	13 ± 6
PCL(2000)(80)BDA-TP1	6.4 ± 3	16 ± 8
PCL(2000)(80)BDA-TP3	7.6 ± 2.3	15 ± 10

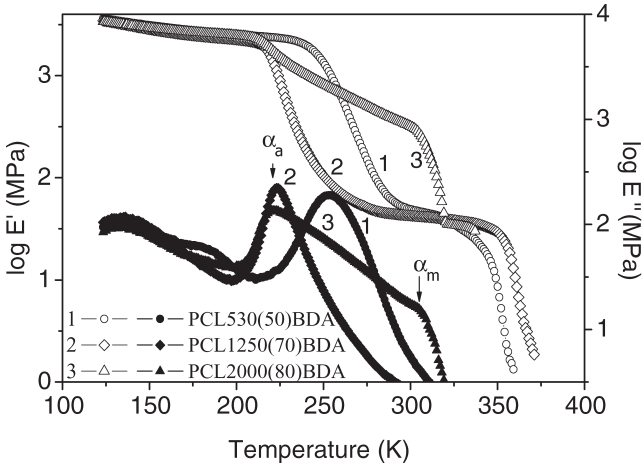

Figure 3.
Temperature dependence of dynamic storage modulus, E′ and dynamic loss modulus, E″ for SPUUs with different PCL M_n.

α_a-absorption and the flow point are very clearly observed for all the polymers.

The α_a-absorption originates from the soft segment phase, while α_m corresponds to the T_m of the soft segment crystallite. The soft segment crystallinity is a very important factor for the value of the storage modulus; higher soft segment crystallinity yields a higher magnitude of E′ at rubber plateau. In SPUUs, degree of soft segment-hard segment phase separation is increased with the increase of soft segment fraction. The PCL(2000)(80)BDA is most likely phase separated. However, the single tanδ peak apparently indicates that these materials are phase mixed. Regardless of the PCL molecular weight, a single tanδ peak is observed (Figure 4).

The tanδ peak temperatures for PCL-(530)(50)BDA, PCL(1250)(70)BDA and

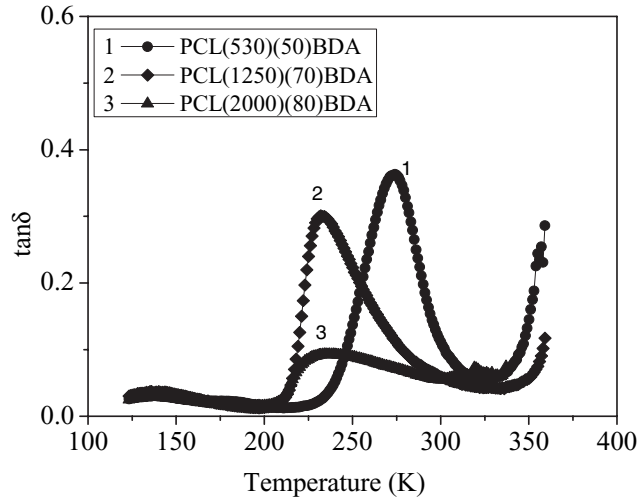

Figure 4.
Tempaerature dependences of tanδ for SPUUs with various PCL.

PCL(2000)(80)BDA are about 260, 235, and 224 K respectively. The tanδ peak temperature increases as the soft segment length decreases. The incremental peak temperature change resulting from the difference in soft segment length is larger for the low molecular weight PCL. The change of peak temperature is 25 K when PCL molecular weight changes from 530 to 1250, and it is 11 K when the molecular weight changes from 1250 to 2000. Essentially similar dependence of soft segment Tg on soft segment length has been reported.[16]

in vitro degradation

The degradation characteristics of the SPUU polymer films in 1 N NaoH at 310 K were investigated. Because the expedited degradation studies of biomaterials in basic solutions were previously reported and correlated to other in vitro methods.[17] The total time taken to degrade 3 different types of polymers such as PCL(530)(50)BDA, PCL(1250)(70)BDA and PCL(2000)(80)BDA was 3, 20 and 96 h respectively. The degradation of SPUU films is a function of molecular

Table 3.
Estimated values of k, n and correlation coefficients for the three systems.

Sample code	k	n	Correlation coefficient
PCL(530)(50)BDA	0.043	0.45	0.99
PCL(1250)(70)BDA	0.028	0.52	0.98
PCL(2000)(80)BDA	0.02	0.55	0.99

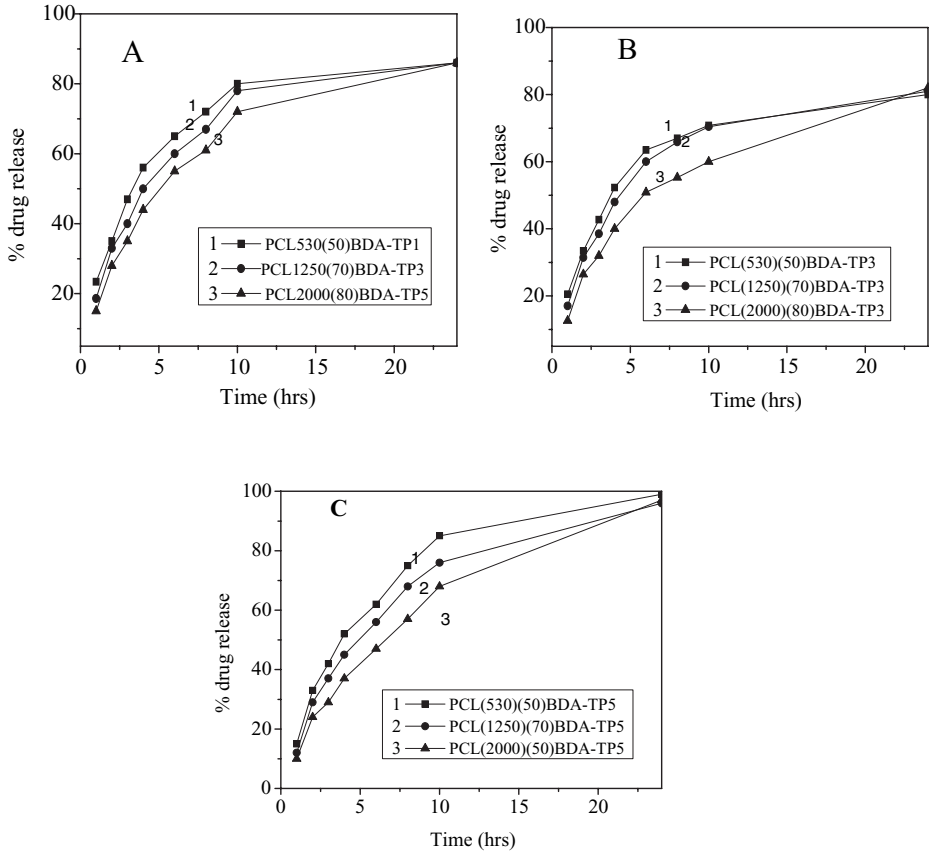

Figure 5.
Drug release versus time curves for different drug loaded SPUUs A) 1% drug loaded, B) 3% drug loaded, C) 5% drug loaded.

weight of the PCL used to prepare SPUU. PCL(530)(50)BDA rapidly degraded into completely water-soluble products within 3 hrs, while the degradation times of the PCL(1250)(70)BDA and PCL(2000)(80)-BDA varied from 1–4 days. The slower degradation rate of PCL(1250)(70)BDA and PCL(2000)(80)BDA is presumably due to the high crystallinity [18] and more hydrophobic nature of higher molecular weight PCL chains in the SPUU blocks. The narrow molecular weight distribution may also be one of the reason for slower degradation of PCL(1250)(70)BDA and PCL(2000)(80)BDA shown in Table 1.

In vitro release

The drug release curves for theophylline-doped (1, 3 and 5 wt %) films in phosphate buffer saline (PBS) pH = 7.4 (PBS) at 310 K are shown in Figure 5(A–C). It is evident that the release from PCL(530)(50)BDA is faster than that of PCL(1250)(70)BDA which is then faster than that of PCL(2000)-(80)BDA, and this result was expected from the increasing hydrophilicity with decreasing PCL content. The release data of the present systems have been further substantiated by fitting the cumulative fraction release data, M_t/M_∞ to an empirical equation 1. Drug release behaviors according to diffusion controlled mechanism are usually governed by Equation (1).

$$M_t/M_\infty = kt^n \quad (1)$$

Where M_∞ is the total amount of the doped drug (M_∞ is generally the total amount of drug released until the system is exhausted). In this study for convenience, M_∞ is approximated by the initial concentration in the matrix). M_t is the drug released until time t after the start of release, k and n are constants. The logarithm of Equation (1) is

$$\log(M_t/M_\infty) = \log(k) + n\log(t) \quad (2)$$

The results displayed in Figure 5(A–C) were fully explained by equation (2). Using the least-squares procedure, we have estimated the values of n and k for the three systems, and these results along with the values of the correlation coefficients are presented in Table 4.

The constant k is related to the release rate, and n to release mechanism.[19] The k values reduces with increase of PCL content in SPUU. The finding that n was approximately 0.5 means the release mechanism was Fickian diffusion controlled.

Conclusion

In this study, PCL based SPUUs were synthesized without the use of catalyst. The effect of PCL molecular weight on the mechanical properties of the SPUUs obtained were discussed. It was shown that SPUUs with lower PCL content in the soft segment have better tensile properties because the inhibition of crystallization of PCL component in soft segment. Finally a model drug theophylline was encapsulated and its *in vitro* release properties were investigated in phosphate buffer saline (PBS) pH = 7.4.

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