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Carbohydrate crosslinked biocompatible polyurethanes: Synthesis, characterization, and drug delivery studies

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ABSTRACT: A series of novel polyurethanes (PUs) with carbohydrate crosslinkers was synthesized. The drug loading and release kinetics were studied by using lamotrigine as a model drug. The polymers were designed in such a way that the drug release was tailored by differences in the stoichiometry of polymers. All the PUs were characterized for thermal and morphological properties by using **differential** scanning calorimetry **and thermogravimetric analysis** and scanning electron microscope**,** respectively. The encapsulation of drug inside PU matrix was confirmed via Fourier transform-infrared (FT-IR) spectra and **scanning electron microscope**. The kinetics and release mechanisms were observed to be a function of stoichiometric parameters such as type of crosslinker, polyol/crosslinker ratio and polyol/chain extender ratio. All the PUs were observed to be non-cytotoxic in normal lung cell line L132. The synthesized PUs exhibited good mechanical strength, tunable release rates and biocompatibility that can be utilized in biomedical applications like wound dressing, biomedical implants**,** and drug delivery carriers. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 42223.

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INTRODUCTION

Polyurethanes are nowadays finding increasing applications as drug delivery carriers in the field of medical science.[1,2] One of the main advantages of polyurethanes in biomedical applications is their flexible chemical structure. A simple modification in stoichiometry and/or raw materials used for synthesis of PU can result in a considerable change in the final polymer properties in order to produce polymers with a broad spectrum of properties ranging from thermoplastic elastic material to rigid thermoset polymer.[3] In addition to that, PUs possess advantages such as adaptability to many different processing conditions, excellent mechanical properties, biostability, biocompatibility, and biodegradability. The degradation characteristics, physical properties, chemical structure, and biocompatible nature of PUs are ideal for the design of the drug delivery devices.[4–7] PUs have been evaluated as drug delivery systems for cancer therapy,[2,8] as scaffolds for tissue engineering,[9] heart valves,[10] and cardiac catheters.[11]

On the other hand, carbohydrates such as starch, cellulose, chitosan, carrageenan, and alginate are finding increasing application as biomaterials, due to their properties like availability, biodegradability, sustainability, lower toxicity, and biocompatibility.[12,13] However, lack of thermal stability, poor solubility and difficult processability are serious limitations for these materials. The incorporation of carbohydrates in the structure of PU can result into synergistic polyurethane with enhanced mechanical properties, thermal stability, and biodegradability.[14] The multiple hydroxyl groups in the carbohydrate structure can be utilized in the synthesis of PUs to confer biomaterial qualities. In the recent past, chemically modified carbohydrates such as hydroxypropyl cellulose[4] and vinyltrimethoxysilane modified starch[15] have been used in synthesis of PU for biomedical application and to achieve enhanced biodegradability, respectively. However, the research focusing unique features of unmodified carbohydrate based polyurethanes intended for use in drug release devices is largely unexplored. We have recently developed a new generation of carbohydrate crosslinked polyurethane and demonstrated their physical, mechanical and thermal characteristics.[14] Hence we decided to utilize versatile properties of polyurethanes along with the benefits of pure carbohydrates as crosslinkers. Various parameters such as NCO/OH (R value), polyol/crosslinker as well as polyol/chain extender ratio were tuned so as to control the drug release kinetics.

Lamotrigine (Figure 1), an antiepileptic agent used for the treatment of seizures, was considered as a model drug. Lamotrigine is known to get rapidly and completely absorbed after oral

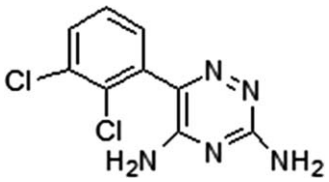


Figure 1. Structure of Lamotrigine.

administration and requires multiple dosing (two to three times daily) for maintaining the therapeutic effect throughout the day. Hence we decided to develop a polymeric system that can deliver lamotrigine in a controlled manner with improved solubility and plasma concentrations over an extended period of time.[16] The effect of stoichiometry of polymers on the release profile of lamotrigine was investigated. There are reports which describe the drug release profile of PUs based on the effect of drug chemistry,[17] molecular weight of polyol,[18] composition of polymer-drug system,[4] and incorporation of ligands in PUs.[19] However, to our knowledge, no report illustrates the effect of mole ratio and stoichiometry of PUs on drug release behavior. We therefore report the synthesis of novel carbohydrate crosslinked polyurethanes as potential controlled drug delivery systems for the first time.

MATERIALS AND METHODS

Materials

Polypropylene glycol (PPG-2000), diethylene glycol (DEG), dibutyltin dilaurate (DBTDL), glucose, cellulose, and starch were purchased from Sigma Aldrich, India. PPG 2000 was dried under vacuum at 100°C for 24 h before use. The carbohydrates were also dried in the oven before use. 2,4-Toluene diisocyanate (2,4-TDI) was kindly donated by GNFC Ltd, India. Tetrahydrofuran (THF) was purchased from Qualigens, Bombay, India. THF was purified by distillation. Lamotrigine was kindly donated by Alembic Ltd, India and it was used directly as received. The buffer solutions of pH 1.2 and 4.5 were prepared as per method reported elsewhere.[20] Sodium chloride, cetyl trimethyl ammonium bromide, potassium dihydrogen phosphate, and phosphate buffer saline tablets (for preparation of pH 7.4 buffer solution) were obtained from Sigma Aldrich, India. Simulated gastric fluid and simulated body fluid were prepared as per procedure described by Marques *et al.*[21]

Preparation of Polyurethane Films

Polyurethane films were synthesized by a prepolymer method using PPG 2000 and 2,4-TDI. Glucose was used as crosslinker and diethylene glycol as a chain extender as well as end capper. In a five-neck reaction kettle equipped with a stirrer, a thermometer, a condenser and nitrogen inlet, 10 g of PPG 2000 was taken. A calculated amount of 2,4-TDI was added drop wise. The reaction was allowed to proceed at 110 to 115°C for 2 h under nitrogen atmosphere. The mixture was then cooled to room temperature. Half of the total calculated amount of chain extender, diethylene glycol, was added under stirring. After 20 min, glucose was added, as dispersion in THF, for crosslinking the polymer. After stirring for 1 h, remaining quantity of diethylene glycol was added to end cap the PU. After 20 min, a catalytic amount of DBTDL was added. THF was added as required during the course of reaction to lower viscosity. Finally, when a certain viscosity was achieved, degassing was carried out and the mixture was transferred to a glass mold. After slow solvent evaporation at room temperature, PU films were dried under vacuum at 60°C for 72 h. A series of PUs corresponding to molar compositions shown in Table I were synthesized. For comparison, PU films were also prepared using starch and cellulose as crosslinkers. The synthesis route of PUs with carbohydrate crosslinker is presented in Scheme 1.

Characterization

The polymers were characterized for mechanical and thermal properties. Tensile strength and % elongation properties of all of the PU films were measured on a universal testing machine (HOUNSFIELD) using test specimen in the form of dumbbells according to IS 3400 (Pt-1)−1987. The testing was carried out using five samples for each PU, and mean values are considered. TGA was recorded on TG–DTA 6300 INCARP EXSTAR 6000 in nitrogen atmosphere in a temperature range of 30 to 450°C, at a heating rate of 10°C/min. Differential scanning calorimetry (DSC) thermograms were recorded on a NETZSCH DSC at a rate of 10°C/min under nitrogen (30–40 mL/min gas flow rate) over a temperature range of −100 to 100°C under both cooling and heating cycles. Scanning electron microscope (SEM) analysis was performed by employing a scanning electron microscope (SEM, JSM 6380LV, JEOL, Japan). The tensile fractured samples were sputter coated with a thin layer of gold. Images of surfaces were taken from the most relevant aspects at different magnifications. To investigate the morphology on the surface of polyurethane films after incorporation of the drug and after release of drug, additional SEM pictures were taken for a representative PU film. The Fourier transform-infrared (FT-IR) spectra of the purified PU, drug loaded PU, and drug were recorded on a PerkinElmer IR spectrophotometer at room temperature. For this purpose, the samples were prepared by solution casting of 2% (w/v) polymer in dimethyl acetamide directly onto KBr pellets. The pellets were then dried at 40°C for 24 h, followed by vacuum drying at 60°C for a further 24 h in order to remove the residual solvent. The pellets thus prepared were then used for FT-IR analysis.

Swelling Studies

The swelling studies of the PUs were carried out in a simulated gastric environment with 0.1*M* HCl solution. The swelling of polymers was measured by the equilibrium weight gain method.[22] Equilibrium swelling (Q) was calculated by using eq. (1), where W_1 is the weight of polymer before swelling and W_2 is the weight of polymer after equilibrium swelling.

$$Q = \left(\frac{W2 - W1}{W1}\right) \times 100 \quad (1)$$

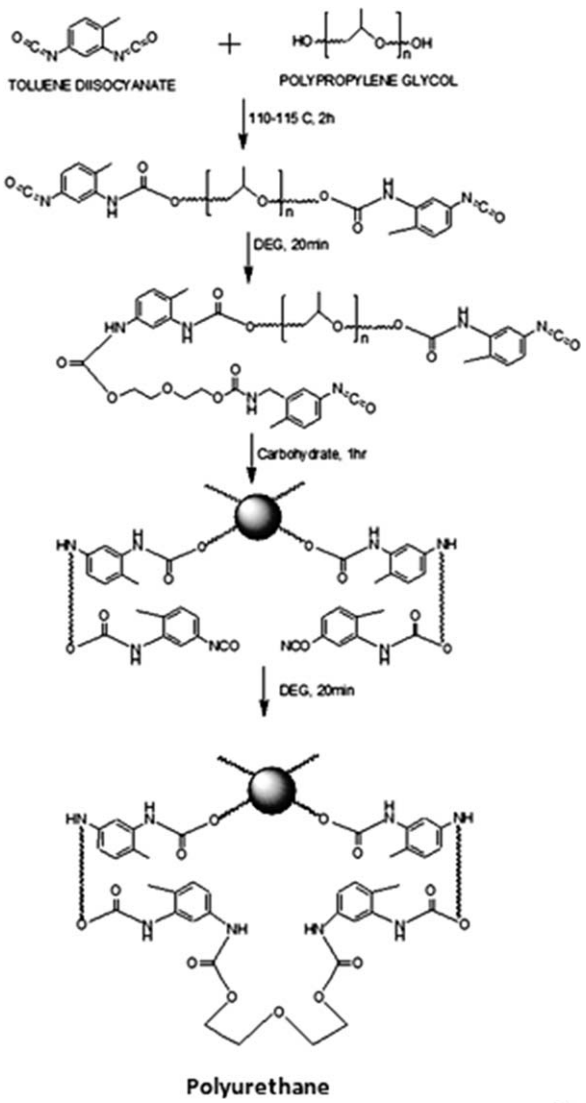
Drug Loading and Release from PUs

Solution sorption method was used for the incorporation of lamotrigine in PU network. Pre-weighed PU film was immersed in 10 mg/mL solution of lamotrigine in ethanol at ambient temperature. The films were allowed to attain swelling equilibrium up to 24 h and then rinsed with 50 : 50 ethanol/water mixture to remove excess drug adhering to the surface of the film. After drying of the films at room temperature till constant

Table I. The Molar Composition, % Hard Segment, and Mechanical Properties of PUs

Code	*R* value NCO/H)	Polyol/crosslinker ratio	Polyol/chain extender ratio	%Hard segment	Elongation (%)	Tensile strength (N/mm^2)
I-A	1.0	1.0	0.25	43.00	538	6.65
I-B	1.0	1.2	0.25	42.23	575	5.82
I-C	1.0	1.5	0.25	41.00	638	3.28
II-D	1.0	2.0	0.50	30.21	600	0.56
II-E	1.2	2.0	0.50	33.06	525	2.53
II-F	1.5	2.0	0.50	36.91	413	2.73
III-Gl	1.0	1.0	0.50	33.29	617	2.44
III- Cel	1.0	1.0	0.50	33.29	663	2.40
III-St	1.0	1.0	0.50	33.29	800	1.02

Gl, glucose; cel, cellulose; St, starch.



Scheme 1. Synthesis of carbohydrate crosslinked polyurethane, corresponds to carbohydrate.

weight, drug loaded PU films were reweighed. The difference in the weight of drug loaded PU film from pure PU film was considered as the amount of drug incorporated into the PU network. The films thus obtained were cut into discs with a diameter of 1 cm and thickness of 100 μm. Films were kept at 4°C in vacuum desiccators until we used it for further study. This method of drug loading has several advantages over other reported methods.[18,23] Firstly, the drug is not being exposed to high temperature during drying. Secondly, the surface adsorption of the drug can be prevented.

0.1*M* HCl solution was used as an external medium to study the release behavior of lamotrigine from the PUs, since 0.1*M* HCl is reported to be a dissolution media for lamotrigine according to the U.S. Food and Drug Administration.[22] A known weight of drug loaded PU films with above mentioned dimensions were immersed in 50 mL, 0.1*M* HCl solution thermostated at 37°C. A constant stirring rate of 100 rpm and temperature of 37°C was maintained throughout the experiment. For measuring the amount of drug release, 1 mL of the sample was taken out from the system at a specific time interval and an equal amount of thermostated 0.1*M* HCl was added to the system immediately. The amount of lamotrigine released was calculated by using a calibration plot obtained at 267 nm on UV spectrophotometer. A similar quantity of corresponding PU without drug, for each polymer, was also kept in 0.1*M* HCl under similar conditions. The absorbance from this polymer was determined for each measurement and it was considered as a blank. The obtained value of absorbance for blank was subtracted from the absorbance value of corresponding drug loaded polymer for all the observations. This was done to ensure that the observations are not affected by the absorbance of any unwanted material leaching out from the polymer during release experiments. All the experiments were performed in triplicate for consistency of results.[23] The average of these measurements was considered for interpretation of data. The drug release was plotted as percentage of cumulative release of the drug at a given time. Data were represented as mean ± standard deviation (SD) of triple measurements. The loading efficiency (%LE) of lamotrigine in the PU film was determined spectrophotometrically from the calibration plot constructed at

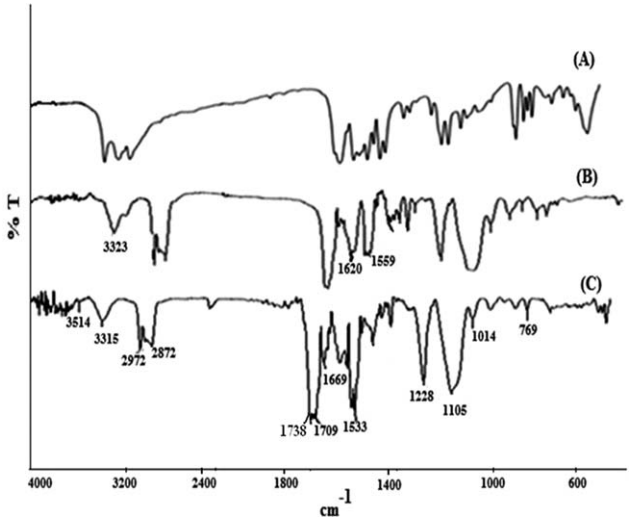


Figure 2. FT-IR spectra of (A) Lamotrigine drug sample, (B) Lamotrigine-loaded PU elastomer and (c) PU elastomer.

267 nm after extensive extraction of drug loaded film in ethanol. Loading percentage was calculated by using following equation.[24]

$$\% \text{ Loading} = \frac{W_{\text{drug}}}{W_{\text{polymer}} + W_{\text{drug}}} \times 100 \qquad (2)$$

where W_{drug} is weight of drug incorporated into PU and W_{polymer} is weight of PU film before drug loading.

Stability Studies

To assess the stability of lamotrigine in 0.1*M* HCl before and after release from PUs, the stability studies were carried out by UV spectrophotometer. The stability of drug solutions both before and after drug release was compared with freshly prepared drug solution of same concentrations at time intervals of 2 h and 24 h at 37°C.

Cell Culture and Measurement of Cell Viability by MTT Assay

The normal lung cell line L132 was obtained from National Centre for Cell Sciences, Pune, India. Cell viability was evaluated by MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide, Sigma–Aldrich) biochemical assay as per a reported procedure.[14,25] Three replicates were performed for each polymer and the mean values are reported.

RESULTS AND DISCUSSION

Mechanical Properties

In our PUs, the carbohydrate crosslinker plays a major role for enhanced mechanical properties for two reasons. Firstly, the physical interaction between carbohydrate and PU allows transfer of stress to the rigid carbohydrate leading to increased mechanical strength.[26] Secondly, the incorporation of carbohydrate into the PU network results in the formation of amorphous polymer-polymer microdomains. This resembles an integrated system formed due to the presence of both, covalent and hydrogen bonds, between the components.[27] As shown in Table I, amongst SET I PUs, the elongation increases as the polyol/crosslinker ratio increases due to increased relaxation of the polymer chains providing flexibility to the resulting PU. This in turn increases elongation property of polymer. Hence PU I-C with highest polyol/crosslinker ratio possesses highest elongation and lowest tensile strength. Tensile strength and elongation exhibited an opposite trend. Amongst SET II PUs, PU II-F with highest *R* value exhibits highest tensile strength and lowest elongation. Polyurethanes with high soft segment content show the elastomeric behavior.[3] This is true in our case for both SET I and SET II PUs. As R value increases, % hard segment also increases (Table I). Excess NCO groups may react with air moisture to form urea crosslinks or they can form allophanate crosslinks with urethane.[28] These two kinds of crosslinks can enhance the tensile strength of PUs. Among SET III PUs the one with glucose and cellulose as crosslinkers showed similar mechanical properties. This is in accordance with our previous report.[14] The starch crosslinked PU showed highest elongation amongst three crosslinkers. This can be explained as follows. While glucose and cellulose, are having linear structure, starch possesses a more branched structure.[29] Due to this, when chain extender DEG and starch compete for reaction with isocyanate, DEG reacts faster due to its linear structure. Thus the chain extender reacted more efficiently and provided higher flexibility to the structure resulting in higher elongation. Probably, that unreacted starch left behind due to slower reaction could bring discontinuity in the polymer matrix which can lead to less tensile strength. Similar result was observed by Desai *et al.*, when mixture of trimethylol propane and starch were used as crosslinkers.[30] It is noteworthy that our PUs possess higher elongation properties, compared with other reported PUs with carbohydrate based nanocomposites,[31–33] carbohydrate blended PU films, and PUs with covalent incorporation of starch derivative.[15]

IR Spectroscopy

Since the basic polyol and diiocynate is same and the crosslinkers are structurally similar the IR spectra of all polymers were almost identical. A representative IR spectrum of PU III-Cel which exhibits highest drug release is presented in Figure 2

along with IR spectra of drug. In PU, the carbonyl absorption band splits into two peaks, at 1707 to 1709 cm^{-1} and 1738 to 1739 cm^{-1}, corresponding to hydrogen-bonded and free carbonyl groups, respectively. Peak at 1669 cm^{-1} was assigned to C—O band of urethane (NH—CO—O). This confirms the crosslinking between the carbohydrate and polyurethane phase. The stretching vibrations of free and hydrogen-bonded N—H groups, are observed at 3514 cm^{-1} and 3315 cm^{-1} respectively.[31,34] The absorption bands at 2972 and 2872 cm^{-1} are associated with C—H stretching vibrations of methylene groups of polyether segments. N—H deformation for amide band is obtained at 1534 cm^{-1}.

An aromatic group of TDI is characterized by multiple weak bands at 1455 cm^{-1} (C—C bonds), as well as at 1297 and 1014 cm^{-1} (C—H bonds). However, there is no unreacted isocyanate in the PU which is confirmed by absence of N=C=O stretching of isocyanate moiety which can arise at 2240 cm^{-1}. The band at 1228 cm^{-1} arises from the urethane functionality (C—O stretch) while the high intensity band at 1105 cm^{-1} is attributed to the C—O stretch for first oxypropylene carbon adjacent to the urethane functional group. The band at 769 cm^{-1} arises from the C—H out of plane vibration of the poly(oxypropylene) portion of the elastomer. Summarizing all the obtained peak values for the synthesized PU, it can be concluded that the PU possesses the chemical structure corresponding to Scheme 1. To investigate spectral changes that may arise due to the incorporation of drug inside PU matrix, the spectra of pure constituents were considered. Incorporation of drug into polyurethane resulted in small frequency shifts, intensity changes and band broadening. This is generally due to intermolecular interactions between constituents like hydrogen bonds between carbonyl, urethane, and hydroxyl groups.[4] It was observed that the bands corresponding to lamotrigine at 3456 cm^{-1} (N—H stretching) was shifted to 3323 cm^{-1} and an extra new band was observed at 1620 cm^{-1}, corresponding to N—H bending vibration as shown in Figure 2(b). The drug entrapment into the PU matrix was ensured by the presence of ring stretching bands due to —C=C— and —C≡N bands of lamotrigine between 1300 and 1500 cm^{-1}.

Morphology

The morphological structures of tensile fractured polyurethane films synthesized in the present study are shown in Figure 3. The SEM pictures of different PU films showed that the polymer surface was non uniform with presence of strings, particles, and bruises. The carbohydrate crosslinkers were identified as tiny white dots distributed nonuniformly across the entire fractured surfaces of the film. This can be compared with the so-called "sea-island structure" proposed by Wu *et al.* for the PUs with cellulose whiskers[35] and Gao *et al.* for PUs with cellulose nanocrystals.[31] The formation of "sea-island structure" in the present case could correspond to the microphase separation between the carbohydrate crosslinkers and the PU matrix. This can be specified by an energy dissipating mechanism on the outer surfaces between carbohydrate crosslinkers and the PU matrix[31] which can lead to the discrepancy in properties of PU films. The "sea-island structure" was observed to be dispersed consistently over the fractured surface of PU.

This further suggests the complete reaction of carbohydrate crosslinkers in the PU matrix and greater compatibility between both. This is attributed to hydrogen bonding interactions occurring between carbohydrate crosslinkers and PU matrix. An important observation is that in case of PU III-St, higher content of the non-uniformly distributed particles was observed showing more "sea-island structures" to appear in the micromorphology of PU III-St (Figure 3). The particles were lesser in case of III-Gl and least observed in case of cellulose PU III-Cel. This is due to variation of the affinity of corresponding carbohydrates to react with the PU matrix as explained in Thickness and Extensibility Section. Since the formation of "sea-island structure" could correspond to the microphase separation between the hard segments and soft segments of PU matrix, starch could provide more phase separation to the corresponding PU as compare to glucose and cellulose. This phenomenon was in agreement with the decrease in tensile strength for PU III-St compared with PU III-Cel and III-Gl.

To study the effect of drug loading and drug release on the morphology of a polymer matrix, PU III-Cel was observed under SEM before drug loading, after drug loading and after drug release (Figure 4). The SEM of PU film without drug shows uniform structure without the presence of voids or cavities. The same film analyzed after drug loading indicates presence of lamotrigine particles with varying size, dispersed in the polyurethane. A similar observation was reported by Huynh *et al.* while reporting the drug delivery studies of chlorhexidine diacetate with polyurethane based system.[36] This ascertains the presence of drug particles entrapped within the PU network. When the drug was completely released, the SEM image of same film showed the layered bruises, nonuniform pores and damaged structure. This is attributed to the vacated space after diffusion of drug particles, leading to severe damage to the PU surface. The degradation study of PUs in 0.1*M* HCl indicated negligible weight loss (approximately 0.05 wt %) after 15days of incubation. This suggests that PUs reported herein show negligible degradation in 0.1*M* HCl. Hence it can be assumed that the damage of PUs observed in SEM analysis was not due to degradation, but significantly due to diffusion of drug.

Thermal Analysis

The thermal stability and decomposition temperature of the urethane bond depends on the composition of PUs. Since the present system utilizes carbohydrate crosslinkers, the thermal degradation of these PUs is expected to be high. However, our previous study revealed that the carbohydrate crosslinked PUs possessed reasonable thermal stability.[13] Similar observation is obtained in the present case also. As shown in Figure 5(A), typical TG curves of the PUs showed weight loss occurring in two stages.[37,38]

The first stage of weight loss in the temperature range between 200 and 390°C can be related with the decomposition of the hard segment. The second stage after 390°C can be attributed to the decomposition of soft segment (Table II). The maximum degradation temperature of all PUs was in the range of 340 to 360°C as shown in Figure 5(B). The thermal stability of all the PUs synthesized herein is observed to be relatively identical.

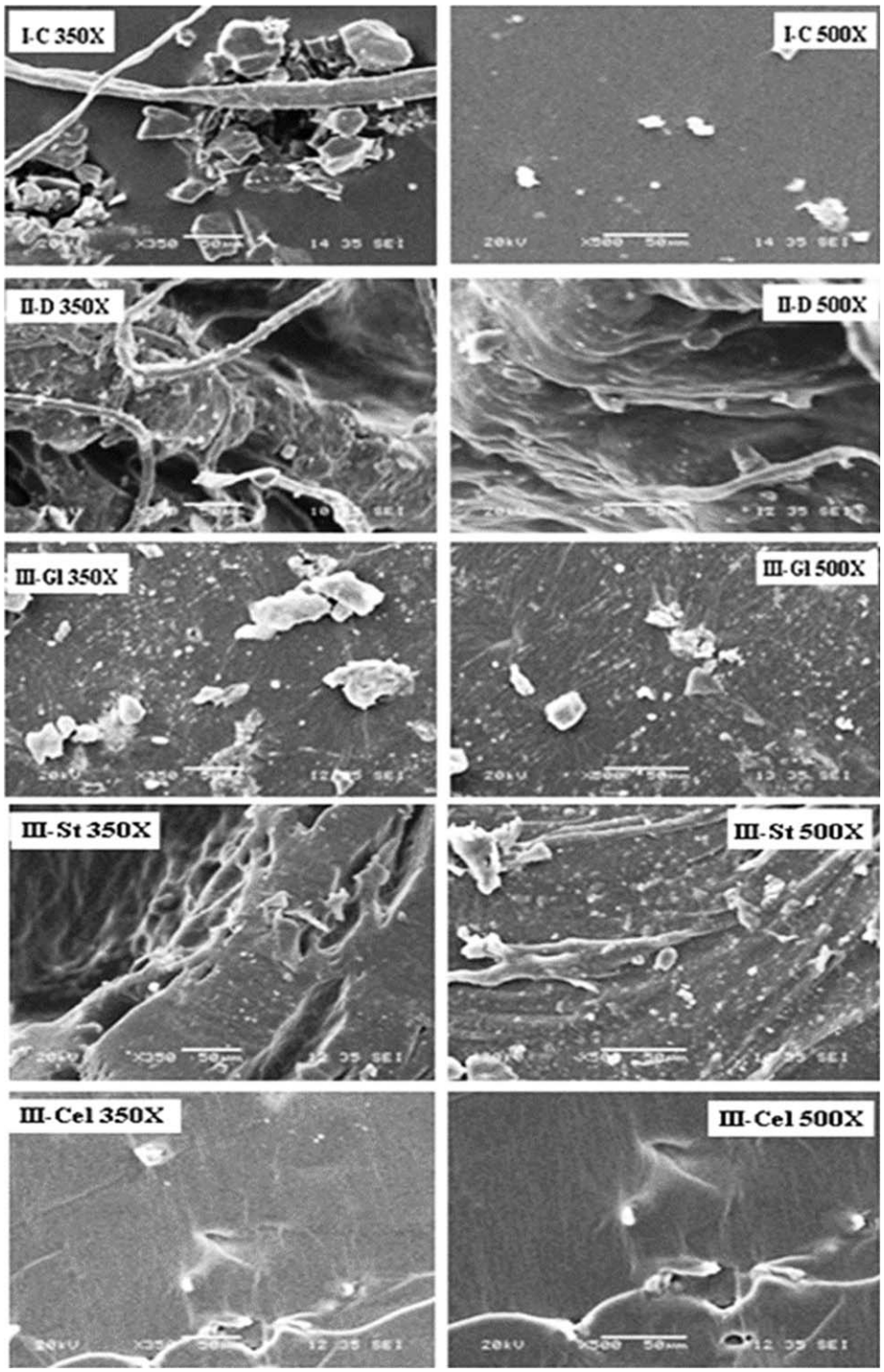


Figure 3. SEM micrographs of various PUs.

DSC thermograms for both heating [Figure 6(A)] and cooling [Figure 6(B)] cycles of the synthesized PUs are shown in Figure 6. The peaks obtained at higher temperature, are the endothermic peaks that can be assigned to glass transition temperature of hard segments (T_{gHS}). On the other hand, the transitions observed at low temperature can be attributed to the glass transition of soft segments (T_{gSS}). The corresponding values are shown in Table III. Amongst SET III PUs, III-St showed the lowest value of T_{gSS} and the value goes on increasing as starch is replaced by glucose and cellulose. The values are in accordance with the mechanical properties as III-St PU possesses higher elongation as a result of higher mobility of polymer chains.

The glass transition of polyurethanes is suggestive of phase segregation and the value of T_g increases with increasing phase mixing.[18] As described in SEM studies, III-St is a polymer

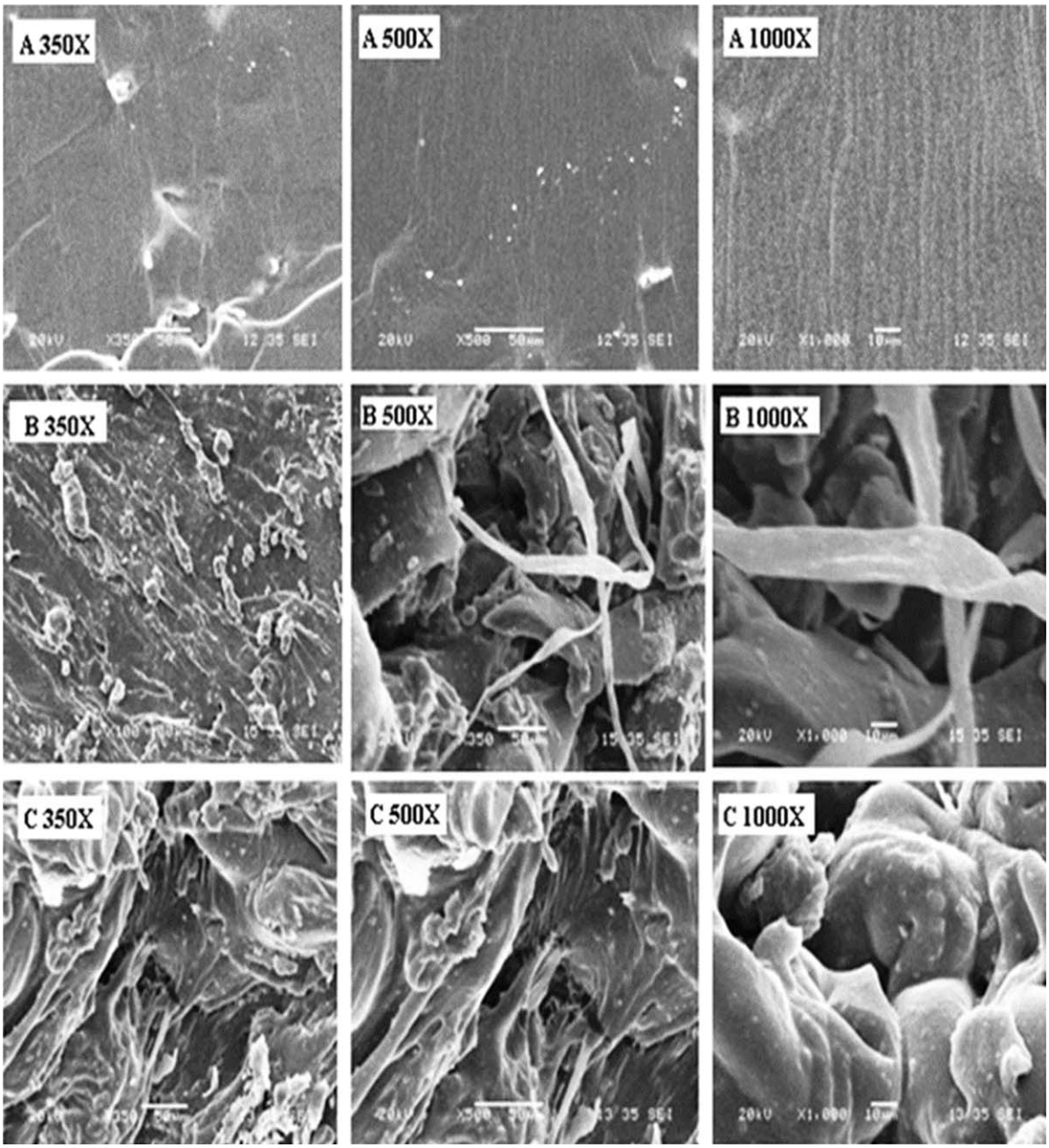


Figure 4. SEM micrographs of PU III-Cel at various magnifications (A) only PU, (B) PU with encapsulated drug, (C) PU after release of drug.

having highest microphase separation of hard and soft domains. As starch is replaced by glucose and cellulose, a small amount of hard segment might be mixed in the soft domains which influence their molecular mobility. This resulted in decreased value of T_g. The endotherm associated with hard segment transition appears at temperature around 50 to 100°C. With increasing hard segment content, the endothermic peaks shift to higher temperatures [Figure 6(B)]. According to Rueda-Larraz *et al.*[3] this indicates that the hard domain is well ordered.

Swelling Studies

Amongst polymer with different polyol/crosslinker ratio, the highest value of Q was found in polymer with highest polyol/crosslinker ratio (1.5). The value of Q goes on decreasing as polyol/crosslinker ratio decreases (Table IV). This is attributed to higher mobility of polymer chains due to increase in soft segment content leading to higher swelling. On the other hand, the value of Q was found to be inversely proportional to the value of R. The swelling studies were also carried out in different media in order to observe the effect of various pH values corresponding to human body and biological fluids on sorption properties of PUs. The results in Table V indicate that no significant difference in equilibrium swelling of PUs was observed when they are subjected to different media.

In Vitro Release

In this study, the percentage loading efficiency is observed to depend on the stoichiometry of synthesized polymers. The data

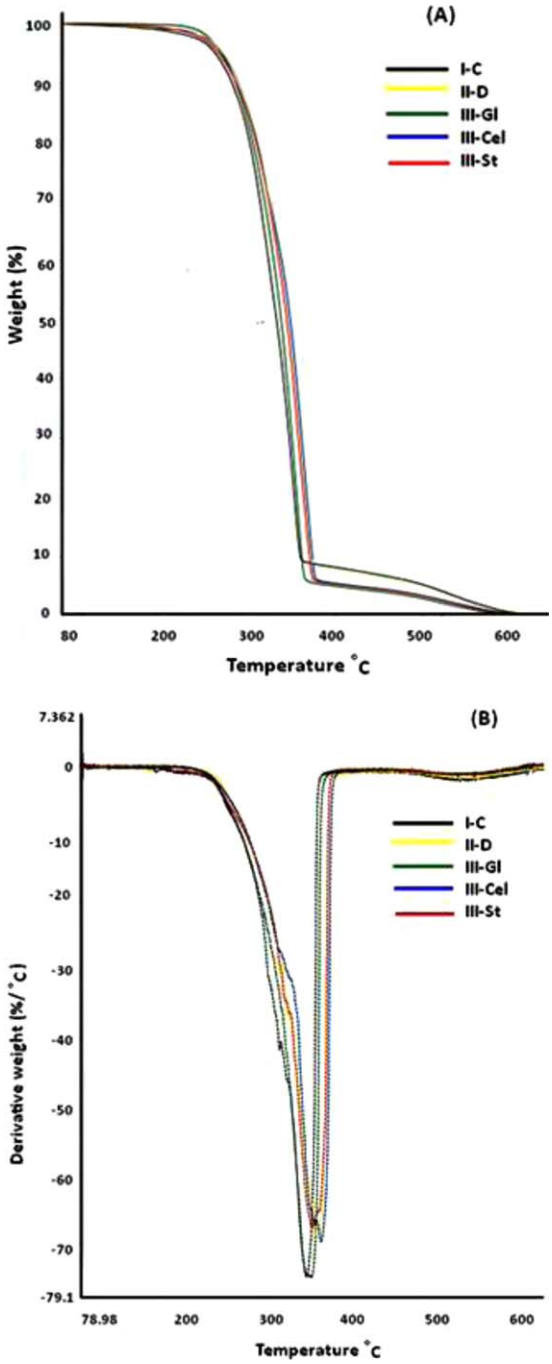


Figure 5. (A) Thermal degradation plots and (B) weight loss derivative versus temperature for PUs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

is compiled in Table IV. For all the polymers, the loading efficiency is directly proportional to rate of swelling. This is expected because swelling of polymer is responsible for drug encapsulation process in the present case. Two important mechanisms have been proposed which determine the release of drug from polymers. (i) Diffusion and (ii) penetration.[4] Although both mechanisms contribute simultaneously to the release process from polymer matrix, a mechanism which verifies a rapid release of the drug will be prevailing.

Table II. Thermal Degradation Temperature of PUs

	Degradation temperature (°C)				
Weight loss (%)	I-C	II-D	III-GI	III-St	III-CeI
1	193.8	212.5	238.8	187.5	204.4
2	233.9	263.0	256.4	269.0	266.2
5	257.4	269.0	266.4	274.4	273.1
20	298.1	305.6	301.9	308.0	307.4
50	329.6	341.4	334.6	342.0	345.1
95	499.5	415.6	402.5	409.3	418.9

According to Singh *et al.*, at low loading (≤5% w/v); in the absence of pores, the drug release will be dominated by a mechanism based on solution-diffusion.[39] Hence this mechanism will be applicable to most of the PUs described herein. While in the case of polymer with higher drug loading (>5%, w/v), the release rate is higher because the cavities get filled with fluid from the environment. This may be another reason for a higher drug release capacity of III-St PU which has the highest drug loading among all systems. Compared with other polymers the mechanism of release of drug from polyurethanes is more complex. This is because, PUs possess a microdomain structure consisting of two different phases; the hard segment and the soft segment. According to Yui *et al.*, among the two distinct phases, one phase acts as a reservoir and another serves as a transport channel, resulting in regulation of the release profile of a drug.[40]

The release of lamotrigine from PUs, as given in Figure 7, shows that the release is very rapid in the beginning and then levels off gradually. The faster release of drug in the initial stage can be attributed to the rapid dissolution and fast diffusion of the drug molecules moving to the outer surface of PU film immediately after immersing into 0.1*M* HCl. The second, slower release is due to swelling of PUs and diffusion of drug molecules. As shown in Figure 7(A), for PUs with variable *R* values, the total percentage cumulative release in 0.1*M* HCl reached up to a maximum of 84.28%, followed by 80.64% and a minimum of 76.7% for PUs with *R* value of 1, 1.2, and 1.5, respectively. The percentage cumulative release was lowest for PU with highest *R* value because high isocyanate content and high hard segment content impart more rigidity to the PU network and slow down the release rate. For PUs with variable polyol/crosslinker ratio, the total percentage cumulative release in 0.1*M* HCl reached up

Table III. Thermal Properties of PUs

Polymer	T_{gSS}	T_{gHS}
I-C	−69.6	74.3
II-D	−47.0	66.2
III-GI	−67.6	70.0
III-St	−75.2	71.5
III-CeI	−47.6	72.5

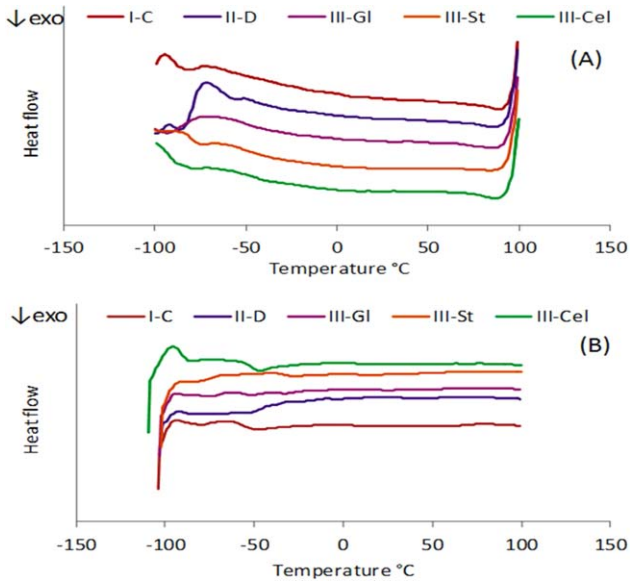


Figure 6. DSC thermograms of PUs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

to a maximum of 85.9%, followed by 72.37% and a minimum of 61.4% for the PUs with polyol/crosslinker ratio 1.5, 1.2, and 1, respectively [Figure 7(B)]. This shows that the lamotrigine could be released in a controlled manner just by tuning the stoichiometry of the PUs. Here it is essential to note that the rate of release of lamotrigine is directly proportional to polyol/crosslinker ratio. This is because high polyol content leads to relaxation of the polymer chains and provides flexibility and enhances the release rate. For similar reasons, PUs with higher polyol/chain extender ratio [Figure 7 (D)] showed higher release (85.9%) compared with PU with the lower one (61.4%).

The release profiles of PUs discussed above are in accordance with the mechanical properties because the release rate is directly proportional to the elongation of PU films and reverse is true for tensile strength.[41] One more important observation is that in all the PUs discussed above, the rate of release of drug is directly proportional to Q value and loading efficiency. This is because of the fact that when drug molecules dispersed in polymers tend to release, the rate of release is in direct relation with both the loading of the drug in the corresponding polymer and swelling efficiency of that polymer.[42,43]

Figure 7(C) is indicative of the release profile of PUs with identical mole ratios and variable crosslinkers. The percentage cumulative release was highest for III-Cel (96.8%) followed by III-Gl (85.9%) and III-St (66.6%). Interestingly, the trend of release of drug in this PUs follows neither the trend of swelling and loading efficiency nor the elongation properties. This can be explained on the base of a fact that the T_g values of PUs are in order of III-St < III-Gl < III- Cel. Drug molecules diffuse faster from polymers with low T_g because of greater free volume and the mobility of the chains. Hence, in SET III PUs, the above explained effect of glass transition temperature dominates over other mechanism for drug release.

Since the PUs studied herein are intended for applications in biomedical field, we also considered study of drug release in different biological fluids and various buffers. Buffer with pH 1.2, 4.5, and 7.4 were selected because they correspond to pH of stomach, stomach small intestine interphase, and blood stream, respectively. Similar studies were carried out in simulated gastric fluid and simulated body fluid. The amount of % cumulative release for all PUs at the end of 10 days has been tabulated (Table VI). It was found that the rate of release was in inverse function of pH of corresponding media. Since the polymers synthesized herein do not contain any component that can trigger pH dependent swelling, all PUs exhibited similar Q values. This suggests that the composition of polymer is not responsible for pH-dependent release of drug. Hence the results obtained herein for variation of drug release with varying pH are attributed to nature of drug. Lamotrigine is compound having amino groups which make it freely soluble in acidic or gastric media.[44] Its solubility decreases with increasing pH, which is the reason for less rate of drug release observed at higher pH.

The drug transport mechanism was studied by using the following equation.[45]

Table IV. Loading Efficiency (%LE), Equilibrium Swelling (Q), and n and k Values for PUs

Code	% LE	Q	n Value	k Value
I-A	2.81	2.35	0.42	0.07
I-B	3.23	4.56	0.45	0.09
I-C	3.69	6.41	0.38	0.10
II-D	4.99	16.49	0.40	0.22
II-E	2.88	6.54	0.40	0.22
II-F	2.38	5.74	0.46	0.18
III-Gl	4.55	8.52	0.35	0.21
III- Cel	3.42	6.95	0.43	0.17
III-St	6.43	11.70	0.43	0.12

n, Value-exponent parameter; k value, kinetic constant for drug release kinetics.

Table V. Effect of Different Media on Swelling Properties of PUs

	Equilibrium swelling (Q) in different media					
Polymer	0.1M HCl	Buffer pH 1.2	Buffer pH 4.5	Buffer pH 7.4	SBF pH 7.25	SGF pH 1.6
I-A	2.35	2.25	2.15	2.13	2.09	2.25
I-B	4.56	4.57	4.64	4.42	4.12	4.42
I-C	6.41	6.39	6.25	6.12	5.91	6.12
II-D	16.49	16.39	15.92	16.22	15.94	16.48
II-E	6.54	6.32	6.55	6.12	5.89	6.25
II-F	5.74	5.56	5.62	5.13	4.89	5.27
III-Gl	8.52	8.68	8.45	8.39	8.12	8.26
III- Cel	6.95	6.89	6.59	6.48	6.21	5.85
III-St	11.7	11.56	11.27	11.65	11.25	11.68

SBF, simulated body fluid; SGF, simulated gastric fluid.

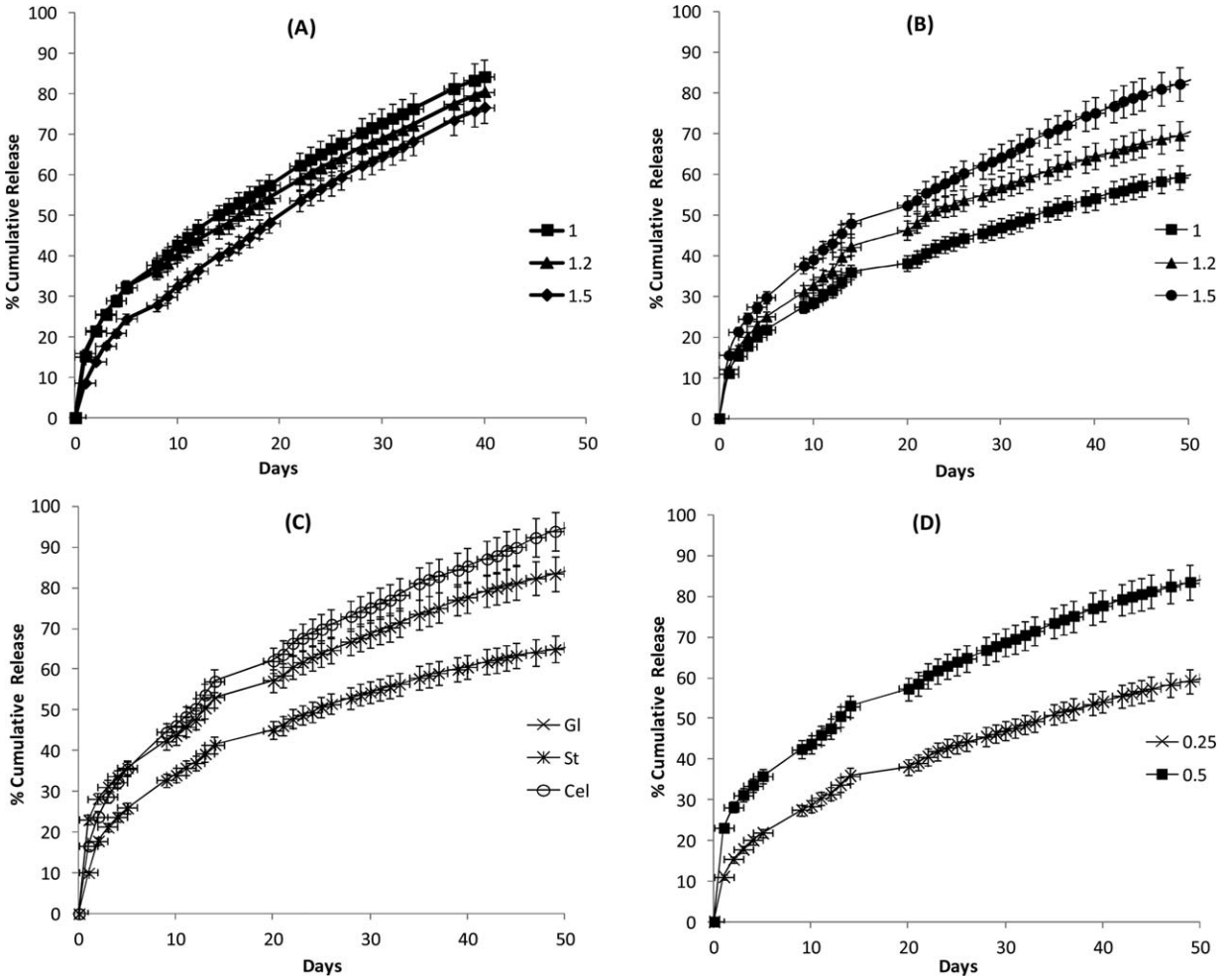


Figure 7. Drug release profiles for studied PU elastomer samples with (A) variable NCO/OH ratio, (B) variable polyol/crosslinker ratios, (C) variable crosslinkers, (D) variable polyol/chain extender ratio.

Table VI. Effect of Various Biological Fluids and Buffers on Drug Release Rate of PUs

	% Cummulative release after 10 days in different release media					
Polymer	0.1*M* HCl	Buffer	SGF	Buffer	SBF	Buffer
		pH 1.2	pH 1.6	pH 4.5	pH 7.25	pH 7.4
I-A	38.13	38.56	37.96	36.21	34.22	33.34
I-B	46.31	46.36	45.66	44.86	42.05	41.01
I-C	52.36	52.98	52.78	50.69	50.02	48.82
II-D	55.95	56.01	55.41	54.63	53.21	51.95
II-E	52.86	53.02	52.32	50.98	49.36	48.17
II-F	48.24	48.36	48.16	47.05	43.12	42.06
III-Gl	45.04	45.82	45.72	44.25	43.21	42.15
III- Cel	62.18	62.53	62.03	61.23	58.96	57.58
III-St	57.26	57.36	56.96	55.23	53.01	51.75

SBF, simulated body fluid; SGF, simulated gastric fluid.

$$\frac{M_t}{M_\infty} = kt^n \quad (3)$$

M_t/M_∞ describes a portion of drug released at time t (M_∞ is considered same as the amount total drug loaded in each

Table VII. Stability Studies of Lamotrigine in 0.1*M* HCl

	Stability before drug release		Stability after drug release	
Polymer	After 2 h	After 24 h	After 2 h	After 24 h
I-A	99.11	99.05	99.15	98.93
I-B	99.26	99.16	99.28	99.04
I-C	98.69	98.59	98.79	98.41
II-D	98.79	98.69	98.59	98.54
II-E	99.65	99.56	99.75	99.48
II-F	99.12	99.01	99.02	98.93
III-Gl	99.68	99.49	99.58	99.41
III-Cel	98.93	98.89	98.97	98.68
III-St	99.23	99.13	99.25	99.05

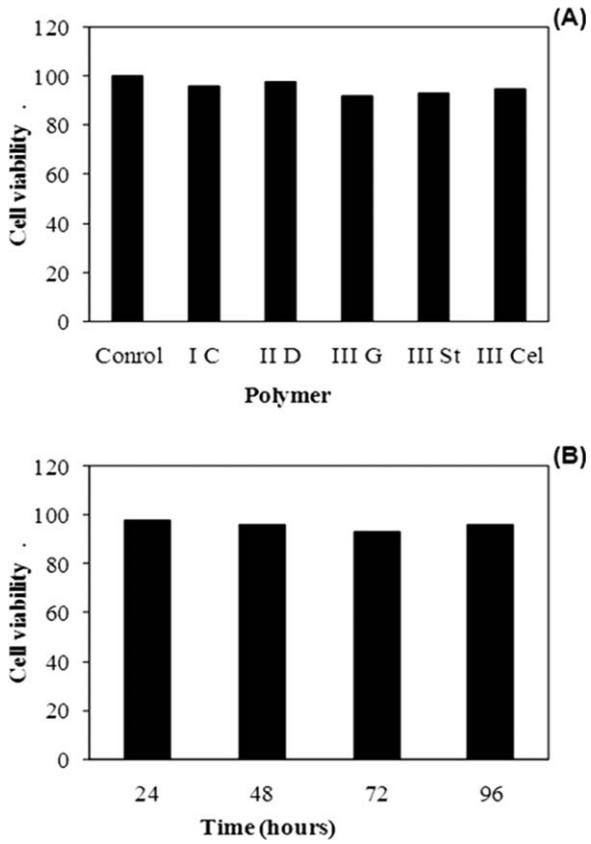


Figure 8. Cell viability by MTT assay of (A) different Pus, (B) PU III-Cel at different time intervals.

polymer), k is constant of release rate, while n denotes an important exponent value which can be used to define release mechanism. Normal Fickian diffusion for a thin polymer membrane is defined by $n < 0.5$, while Case II transport is characterized by $n = 1.0$. The results obtained from the plot shown in Figure 7, were used to plot a graph of log (M_t/M_∞) versus log (t). Using a linear regression, the intercept and slope was determined which gave values of k and n respectively. All release profiles presented n values that are less than 0.5 as listed in Table IV, which suggests that the release of lamotrigine from the synthesized PUs herein follows the Fickian diffusion.

Stability Studies

The results obtained for stability studies have been listed in Table VII. The results suggest that the stability of lamotrigine is not affected after drug release in 0.1*M* HCl solution.

Cell Viability by MTT Assay

The nontoxicity of some polyurethanes against normal lung cell line L132 was confirmed by MTT assay. The representative results in Figure 8 show that even after 96 h the MTT absorbance of the media exposed to PUs was almost equal to control and well below the toxicity limit. This indicated that there was no leaching of harmful toxins from PUs under study. All PUs were observed to be noncytotoxic. Hence this set of noncytotoxic PUs can be used as drug carriers. The PUs reported herein showed no toxic effect, however, the PUs having TDI as an ingredient may degrade to give poisonous product that may harm human tissues. Hence a study of *in vivo* biodegradation and biocompatibility of the reported PUs is essential and will be carried out in near future.

CONCLUSIONS

The drug release rate of glucose crosslinked PUs could be modified by a small change in content of hard/soft segment. The rate of release of lamotrigine was directly proportional to polyol/crosslinker ratio and polyol/chain extender ratio and inversely proportional to the NCO/OH ratio. These results indicate that control of structural design of PUs can allow control of the drug release from the polyurethane matrix. These biocompatible PUs offer an attractive application for controlled release of biologically active agents.

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