Summary of the thesis

Synthesis of Biocompatible Polyurethanes for Drug Delivery Applications

To be submitted to
The M. S. University of Baroda

For the degree of
DOCTOR OF PHILOSOPHY
In
Chemistry

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March 2016

The thesis is divided into five chapters.

Chapter 1: Introduction

The origin of polyurethanes (PUs) began in 1937 at I.G. Farbenindutrie where Otto Bayer, also called "father" of polyurethanes, and his co-workers performed the addition polymerization reaction between diisocyanates and diols. The term "polyurethane" is confusing since the name may mean that PUs are either polymers obtained by polymerization of methane or these are polymers containing urethane groups as monomers; neither of the meaning is true! The PUs are the polymers with the plurality of urethane groups in the molecular backbone, regardless of the chemical composition of the rest of the chain. PUs are important versatile polymers varying from flexible thermoplastics to rigid thermosets, obtained by step growth polymerization between diisocyanate or polyisocyanate with isocyanate (-NCO) functional group and hydroxyl terminated oligomer (polyol) having at least two reactive hydrogen atoms (Fig.1). The common components used in PU synthesis are listed in Table 1.

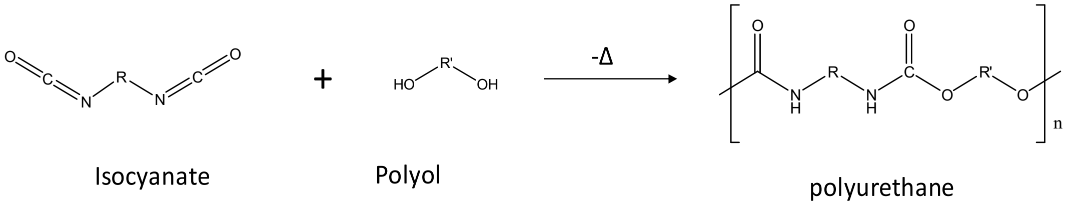
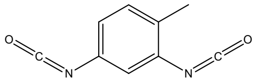
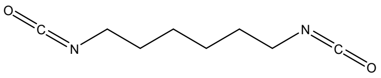
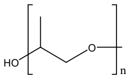
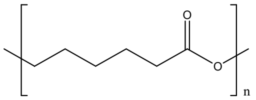
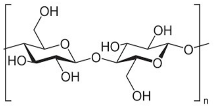


Figure 1 Chemical reaction of Polyurethane formation

PUs can be either thermoplastic or irreversibly thermoset depending upon its structure. For example, the PUs synthesized from diisocyanate and a bi-functional polyol results in thermoplastic PU, whereas introduction of crosslinkers with more than two functional groups will yield thermoset PUs with three dimensional crosslinking (Fig.2). If the initial concentration of isocyanate is higher than polyol, the prepolymer obtained by reaction between them is said to be NCO-terminated prepolymer which can further react with other crosslinker/chain extender or other chemicals that are prone to react with NCO functional groups.

Table 1 List and details of common components in PUs

Component	**Type**	**Examples**	**Structure**
Diisocyanate	Aromatic	Toluene-2,4-diisocyanate (TDI)	
	Aliphatic	Hexamethylene diisocyanate (HMDI) /1,6-diisocyanatohexane	
Polyols	Polyether	Polypropylene glycols	
	Polyester	Polyester polyol of diacid and diol	
Crosslinkers	Hydroxylated	Carbohydrates	

Polyurethanes and biocompatibility

PUs are usually obtained from reaction between polyfunctional alcohols and polyisocyanate forming urethane linkages. PUs have been used for various biomedical applications due to their appreciable physical and mechanical properties and good biocompatibility. For some of these applications such as vascular prostheses, artificial skin, pericardial patches, soft-tissue adhesive, drug delivery devices, scaffolds for tissue engineering, besides biocompatibility, biodegradability is a must have factor. Biodegradability of polyurethanes is generally achieved by incorporating labile and hydrolysable moieties into the polymer backbone. The most common method for fulfilling this goal is the application of polyols (soft segments) with hydrolysable bonds as starting materials for the preparation of polyurethanes. Several hydroxyl terminated polymers such as polycarolactone, polyalkylene adipate, polylactides, polyglycolides were used for the synthesis of hydrolytically degradable polyurethanes. The preparation of polymers from renewable sources such as vegetable oil-based materials is currently of great interest.

Use of carbohydrates as crosslinkers in PU synthesis

Carbohydrates are abundant and inexpensive renewable resources. Being multihydroxyl compounds they can easily serve the purpose of a crosslinkers for PUs. 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. 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 polyurethane with enhanced mechanical properties, thermal stability and biodegradability. 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 and vinyltrimethoxysilane modified starch 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.

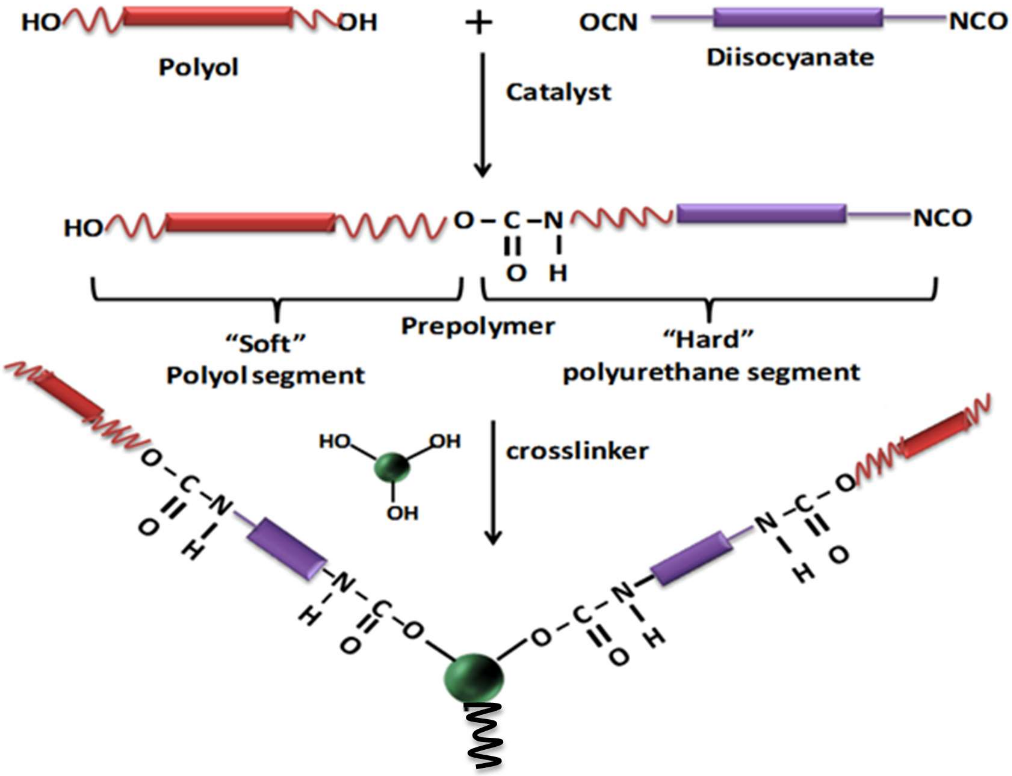


Figure 2 Synthesis of crosslinked PU elastomer

Application of polyurethanes in drug delivery systems

Over the past decades, considerable interests have been directed towards the design of switchable drug delivery implant, which is capable of providing on-demand drug release to the diseased site. In clinical situations, such novel drug delivery device is particularly applicable for local and intermittent therapeutics, e.g. in the treatment of post-surgical pain, localized infection and solid tumors, where the severity of disease symptoms often fluctuates with time, and thus on-demand drug delivery from an implant at the diseased site could enhance therapeutic efficiency and concurrently minimize toxic side effects commonly associated with anesthetic/antibiotic/ anticancer agents. In general, an ideal on-demand drug delivery device should release little or no drug in the off state, be reproducibly switchable to the on state without mechanical disruption and then release a tuneable dosage of drug to surroundings. 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. In addition to that, PUs possess advantages such as adaptability to many different processing conditions, excellent mechanical properties, biostability, biocompatibility and biodegradability.

Chapter-2: Structure–property relationships and biocompatibility of carbohydrate crosslinked polyurethanes

Biocompatible and biodegradable polyurethanes (PUs) based on castor oil and polypropylene glycols (PPGs) were prepared using various carbohydrate crosslinkers: monosaccharide (glucose), disaccharide (sucrose) and polysaccharides (starch and cellulose). Compared to polyols, variations in chain extenders and crosslinkers for enhancing biodegradability of polyurethanes have been reported to a less extent.

Hence we decided to use multi hydroxyl carbohydrates as crosslinkers in PU system which is likely to offer following advantages.

1. Enhance both degradability and mechanical properties of polymer
2. Provide multifunctional sites to form randomly crosslinked networks
3. Nontoxic, inexpensive, readily available from renewable resources

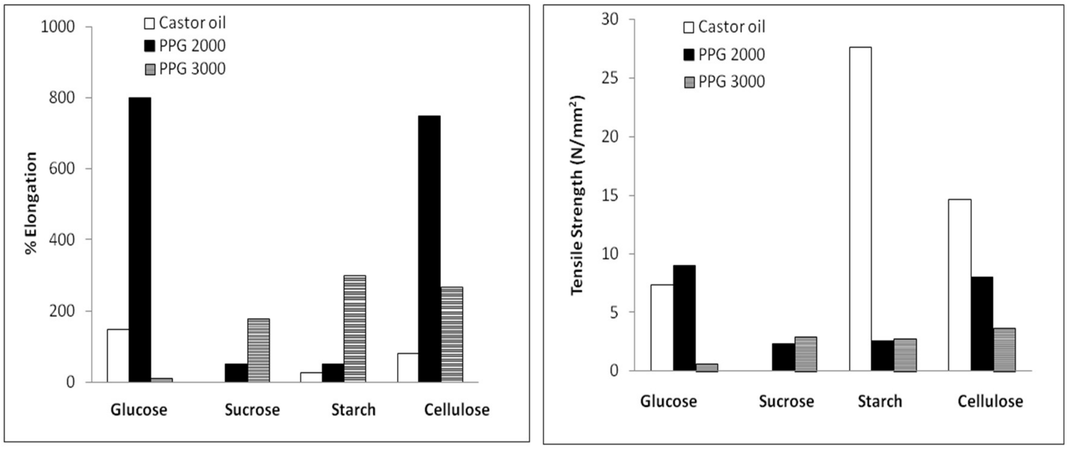


Figure 3 Effect of variation of polyols and carbohydrates on (a) % Elongation and (b) tensile strength of polyurethanes

The mechanical and thermal properties were investigated and interpreted on the basis of SEM study. The advantage of incorporating various carbohydrates is to have tunable mechanical properties and biodegradability due to variety in their structure. The glass transition temperature and sorption behaviour were dominated by the type of polyol than by the type of crosslinker. All the PUs were observed to be biodegradable as well as non-cytotoxic as revealed by MTT assay in normal lung cell line L132.

As shown in Fig.3, when polysaccharides are used as crosslinkers the elongation is higher in PPG based PUs while tensile strength shows reverse trend. Higher molecular weight of polyol tends to increase the flexibility due to multiple -CH_2

groups and hence a tremendous loss in mechanical strength of PPG 3000 based PUs especially when glucose is used as crosslinker. Castor oil system having starch as a crosslinker showed maximum value for tensile strength. The results of mechanical properties could be explained on the basis of SEM morphology of tensile fractured sample.

The study reveals that carbohydrates can be promising crosslinkers for synthesis of polyurethanes. The performance of the carbohydrate was dependent not only on its structure but also on the type of polyol. With a combination of polyols and carbohydrates a wide spectrum of significant mechanical properties can be achieved which can be further tuned by varying the NCO/OH ratio and polyol/crosslinker ratio. The resulting PUs possessed reasonable thermal stability and interesting sorption properties. Thus this work rendered a strategy for achieving high mechanical performance along with biodegradability and biocompatibility for potential applications as drug delivery systems.

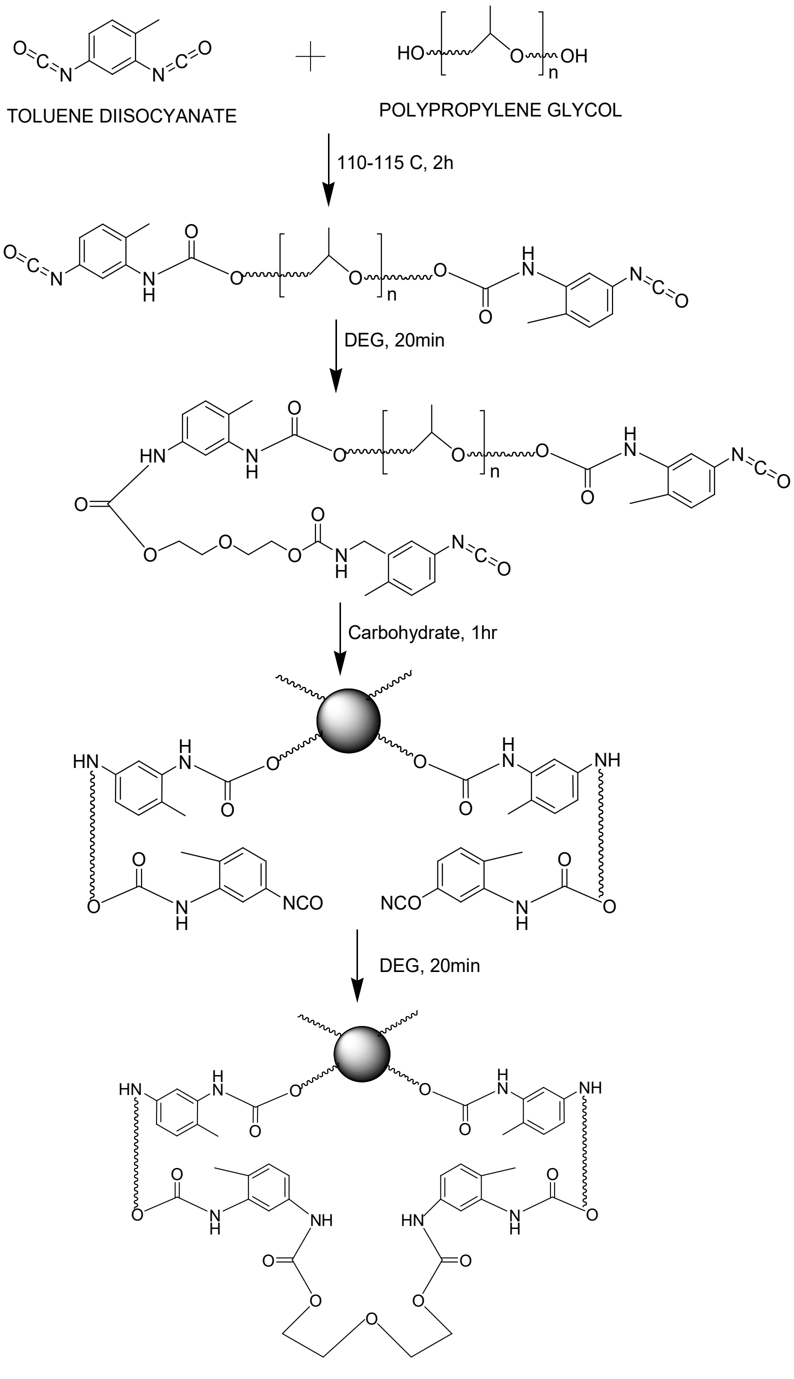
Table 2 List of the techniques used for determination of properties of PUs

Sr no	Techniques / Instrument used	Properties
1	Universal Testing Machine	Mechanical properties
2	Thermo gravimetric analysis (TGA) and Differential scanning calorimetry (DSC)	Thermal properties
3	Scanning electron microscopy (SEM)	Morphology
4	Fourier transform infrared spectroscopy (FT-IR)	Structural elucidation
5	UV-vis-nIR Spectroscopy	Drug release profile

Chapter-3: Stoichiometry of PUs - A commanding factor on the rate of delivery

A series of novel polyurethanes (PUs) with carbohydrate crosslinkers was synthesized (scheme 1). 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 DSC & TGA and SEM respectively. The encapsulation of drug inside PU matrix was confirmed via FTIR and SEM. 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. A representative IR spectrum of PU III- Cel which exhibits highest drug release is presented in Fig. 4 along with IR spectra of drug. In PU, the carbonyl absorption band splits into two peaks, at 1707–1709 cm^{-1} and 1738–1739 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.



Scheme 1 Synthesis of carbohydrate crosslinked PU

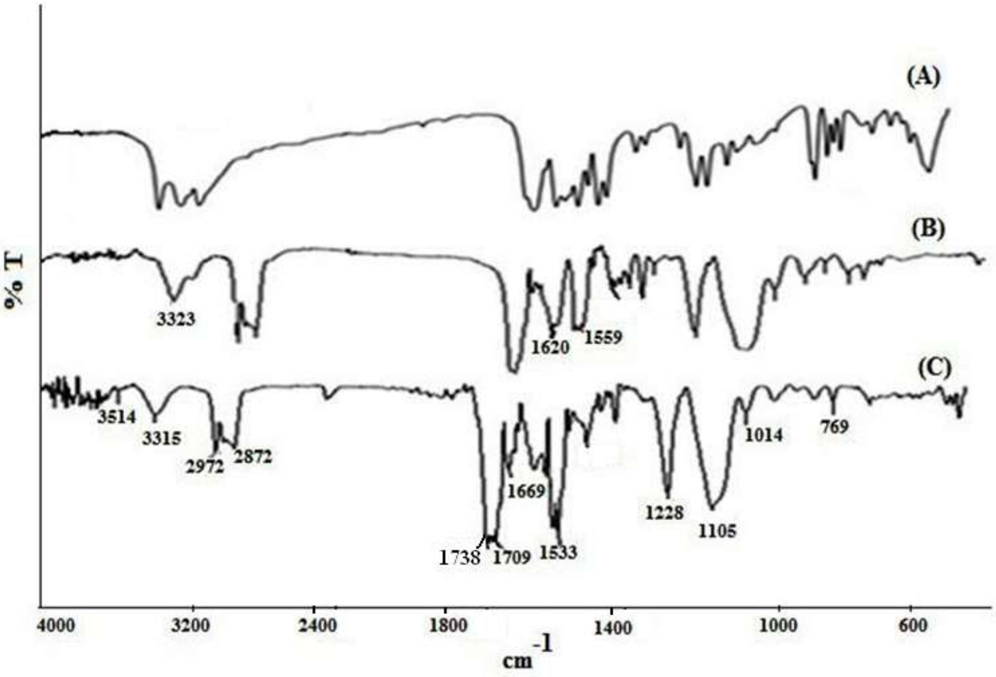


Figure 4 FT-IR spectra of (a) Lamotrigine drug sample, (b) Lamotrigine loaded PU film (III-Cel) and (c) III-Cel PU film.

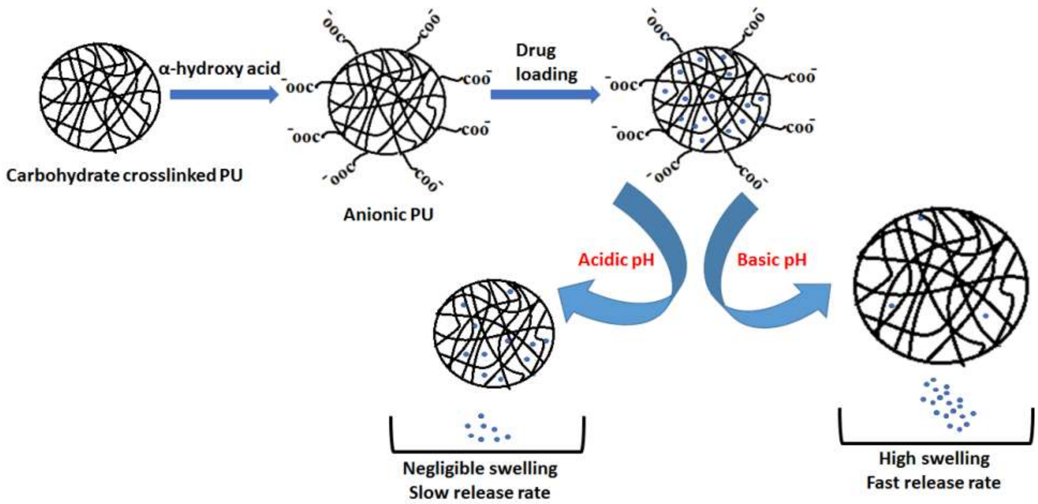
To study the effect of drug loading and drug release on the morphology of a polymer matrix, PU III-Cel was observed under SEM before drug loading, after drug loading and after drug release (Fig. 5). The SEM of PU film without drug shows uniform structure without the presence of voids or cavities. The same film analyzed after drug loading indicates presence of lamotrigine particles with varying size, dispersed in the polyurethane. 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, non-uniform 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 drug release rate of glucose crosslinked PUs could be modified by a small change in content of hard/soft segment. As shown in scheme 2, the rate of release of lamotrigine was directly proportional to polyol/crosslinker ratio & 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.

Chapter-4: Cellulose crosslinked pH-responsive waterborne polyurethanes for drug delivery: Alpha-hydroxy acids as drug release modifiers

Cellulose crosslinked waterborne polyurethanes (PUs) based on poly ε-caprolactone with lactic acid (LAPU)/ glycolic acid (GAPU) / dimethylol-propionic acid (DAPU) as a drug release modifiers cum chain extenders were prepared. PUs were loaded with felodipine and drug release was monitored at different pH values. The selection of α-hydroxy-acids like lactic acid, glycolic acid and dimethylol propionic acid for incorporation in the structure of PUs was done on the basis of the nature of hydroxyl groups. Moreover, the difference in their pKa values, chemical structure, polarity and affinity towards reaction with NCO of isocyante allows detecting the critical parameters towards the drug release efficiency of the resulting PU. With a view to control volatile organic compound emissions in the form of solvent for PU synthesis and its increasing costs, we synthesized waterborne polyurethanes in the present study. The structure of the polymers was characterized by FTIR, DSC & TGA and SEM.

The drug release study was carried out at three different pH values i.e. 1.2, 4.5 and 7.4 for all the polymers. The rate of release of the drug was increased when the pH of buffer increased from 1.2 to 4.5 and again increased when pH was 7.4.



Scheme 2 Mechanism of drug release form pH responsive PUs

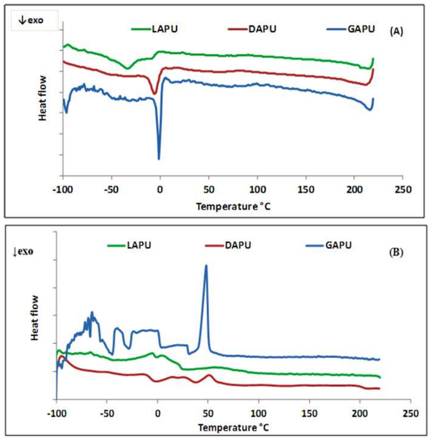


Figure 6 DSC thermograms of PUs

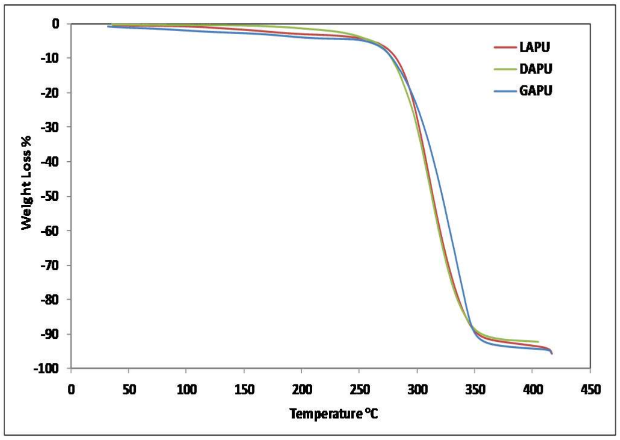


Figure 7 Thermal degradation plots of PUs

The pH responsiveness of the PUs was attributed to acid chain extenders that forms anionic polymer when subjected to PBS. At pH 1.2, the release of the drug was observed due to swelling in PBS. The response with respect to pH is triggered due to presence of insoluble -COOH groups that get ionized at pH 4.5. As shown in scheme 2, the presence of a large number of anionic groups on the polymer makes the polymer chains repel one-another leading to expanded dimension or higher swelling of the polymer. The phenomenon becomes more effective when the pH increases to 7.4, leading to highest rate of drug release at that pH.

It was observed that T_{gSS} for PUs was highest for GAPU, followed by DAPU and LAPU. This can be explained on the basis of the fact that the glass transition temperature of PUs depends strongly on the molecular mobility. The polyurethane with high crosslinked structure results into the lower mobility of chains resulting into high T_g. The PUs were analyzed for thermal degradation behavior using TGA (Fig 7).The thermal degradation, structural and morphological properties of all PUs were identical, irrespective of type of chain extender. GAPU with highest crosslinked structure showed highest T_g and slowest drug release at a given pH. All PUs showed the highest release rate at pH 7.4, considered to be pH of human organs such as the colon as well as vagina after sexual intercourse. The reported PUs, being “smart” polymers, can find attractive application in the field of drug delivery involving pH responsive characteristics such as microbicides and vaginal passaries for prevention of HIV-AIDS and other sexually transmitted diseases.

Chapter-5: β-Cyclodextrin-polyurethane magnetic nanoconjugates for targeted drug delivery in cancer therapy

β-Cyclodextrin was conjugated with diisocyanate modified magnetic nanoparticles (MNPs) through urethane linkages to obtain magnetic nanoconjugates. The crosslink density of polyurethane could be varied by changing the concentration of β-Cyclodextrin. The nanoparticles were characterized for thermal, magnetic and structural properties by using TGA & DSC, VSM and FTIR respectively. Scanning Electron Microscope-Energy Dispersive X Ray Spectrometry (SEM-EDS) and XRD were used to study the morphology and changes in crystalline nature of MNPs respectively. Dacarbazine, an anticancer drug was considered as a model drug for loading and release studies. It was observed that by controlling the stoichiometry of PU, the surface accessible inclusion sites of cyclodextrin could be controlled thereby achieving command over entrapment efficiency and release behavior of MNPs. All the nanoparticles were observed to be non-cytotoxic as revealed by MTT assay. The prepared nanocarriers thus can provide a strong platform for magnetic tumor targeting under guidance of magnetic field and through cyclodextin-drug complexation.

Fig 8 shows the release profiles of dacarbazine-loaded PEG-PU-NPs and CYD-PU-NPs as a function of time. It was observed that PEG-PU-NPs showed higher rate of drug release as compared to CYD-PU-NPs. The drug was released within a shorter period of time with a burst type of release (initial rapid release of 45% of drug release during first 40 min) in case of PEG-PU-NPs. This is attributed to higher swelling coefficient of PEG-PU as compared to CYD-PU. The drug release in case of PEG-PU-NPs thus follows diffusion mechanism as observed for other reported polyurethanes. However, in case of CYD-PU-NPs, the drug release behaviour was entirely different as it was observed to be slower and sustained. For CYD-PU-NPs, the drug release profile was characterized by an initial rapid release of 5-15% of drug release during first 20-25 min followed by comparatively slower rate of release of remaining drug

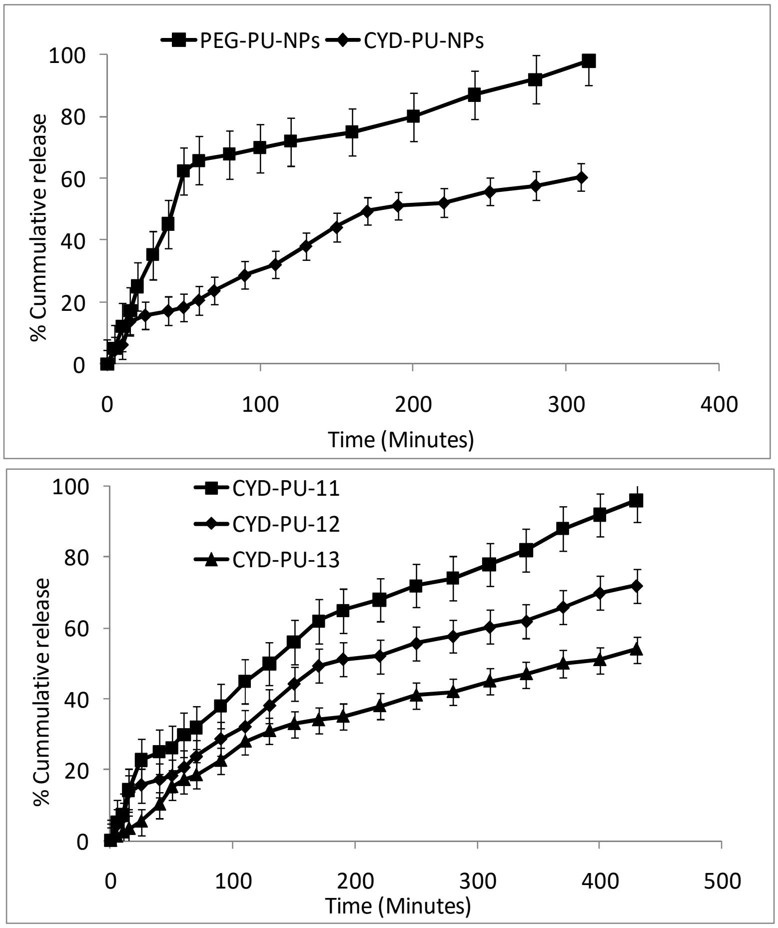


Figure 8 Drug release profiles of PU nanoconjugates

. This observation suggests that a portion of the drug-cyclodextrin complex in the nanoparticles is quite labile and the rest portion is apparently stable. In case of CYD-PU-NPs, in addition to diffusion mechanism of CYD-PU, the role of cyclodextrin as a host to form drug-cyclodextrin complex formation also plays an important role in release of drug. The labile portion is thus hypothesized to be released due to the swelling effect of the polyurethane while later sustained and slower release is attributed to dissociation of drug-cyclodextrin complex. The hydrophobic part of dacarbazine interacts with hydrophobic cavity of β-Cyclodextrin which may lead to higher stabilization of drug-cyclodextrin complex contributing in slowing the release down. During the course of 430 min, the total percentage of cummulative release observed was 54%, 72% and 96% for CYD-PU-11, CYD-PU-12 and CYD-PU-13 respectively. The reduction in release rate is due to enhanced capacity of cyclodextrin to provide better hosting to encapsulated drug due to smaller cavity size in case of CYD-PU-11. Since diffusion of drug from smaller cavity may be more resistive as compared to bigger cavity the rate of drug release was compromised.

Conclusion

Our studies are aimed at synthesis and characterization of novel carbohydrate crosslinked polyurethanes and to further explore their application as drug delivery devices. A variety of polyols ranging from synthetic polyols like polypropylene glycols of different molecular weights to the bio-based polyol like castor oil have been used to demonstrate effect of polyols on structure and properties of PUs. Similarly, a range of carbohydrates starting from monosaccharide such as glucose to disaccharide like sucrose and polysaccharides like starch and cellulose and supra molecule cyclodextrine have been utilized as a crosslinkers into the PU network in order to observe the effect on PUs implied by carbohydrate crosslinkers. The effect of variation of stoichiometry of PU components on their drug release properties has been studied. Furthermore, stimuli-sensitive polyurethanes were prepared by introduction of α-hydroxy acids into the PUs. This resulted into pH-responsive as a function of α-hydroxy acids-drug release modifiers. The PUs showed higher drug release at pH 7.4 and lowest release at pH 4.5. Drug nano-carriers which respond to external magnetic field were developed using β-cyclodextrin. Of interest, is the application of these materials to accommodate and release a wide variety of drugs in response to the properties of polymers or effect of external stimuli. A variety of drugs like antiepileptic, anti-hypertension and anticancer drugs have been used as model drugs.

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10. M. H. Mohamed, L. D. Wilson, & J. V. Headley, Carbohydrate Polymers, 80(1) (2010), 186–196.

List of Publications

Research Papers

1. **A. Solanki** & S. Thakore, β-Cyclodextrin based magnetic nanoconjugates for targeted drug delivery in cancer therapy, *RSC Advances*, 6 **(2016)** 98693-98707.
2. **A. Solanki** & S. Thakore, Cellulose crosslinked pH-responsive waterborne polyurethanes for controlled drug delivery: Use of α-hydroxy acids as drug release modifiers*, International Journal of Biological Macromolecules,* 80 **(2015)** 683–691.
3. **A. Solanki**, B. Kamath & S. Thakore, Carbohydrate crosslinked biocompatible polyurethanes: Synthesis, characterization and drug delivery studies, *Journal of Applied Polymer Science*, 132 **(2015)** 42223.
4. **A. Solanki**, J. Mehta & S. Thakore, Structure-property relationships and biocompatibility of carbohydrate crosslinked polyurethanes, *Carbohydrate Polymers*, 110 **(2014)** 338–344.
5. **A. Solanki**, J. Mehta, Development of Green Polyurethanes with Bio-Crosslinkers, *European Polyurethane Journal*, July **2013.**