Synthesis and Characterization of Methoxypolyethyleneglycol and Lauric Acid Grafted Novel Polyurethanes for Controlled Release of Nifedipine

Namdev B. Shelke, Tejraj M. Aminabhavi

Drug Delivery Division, Center of Excellence in Polymer Science, Karnatak University, Dharwad, Karnataka 580 003, India

Received 16 August 2006; accepted 5 November 2006
DOI 10.1002/app.25822
Published online 26 April 2007 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Novel polyurethanes (PUs) grafted with methoxypolyethyleneglycol (mPEG) and lauric acid (LA) were synthesized by solution polymerization using dibutyl tin dilaurate as a catalyst, taking different molar ratios of LA-trimethylol propane (LA-TMP) with respect to mPEG-trimethylol propane (mPEG-TMP). The polymers obtained were characterized by Fourier transform infrared spectroscopy and gel permeation chromatography to confirm, respectively, the PU formation and molecular weight. Moderate molecular-weight PUs were obtained, and nifedipine (NFD)-loaded microspheres were prepared by solvent evaporation method. The size of the microspheres as measured by laser light scattering technique ranged between 10 and 50 μm. An increase in the size of particles was observed with an increasing molar ratio of mPEG-TMP with respect to LA-TMP. The % encapsulation efficiency was found to vary between 65 and 92. The surface morphology of microspheres as studied by scanning electron microscopy revealed the spherical nature of the particles with wrinkles on their surfaces. Crystalline nature of the drug in the microspheres after loading was studied by X-ray diffraction technique. The release of NFD through the matrix microspheres was investigated in pH-7.4 phosphate buffer. An increase in release rate was observed with increasing molar ratio of mPEG-TMP with respect to LA-TMP. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 105: 2155–2163, 2007

Key words: methoxypolyethyleneglycol; lauric acid; trimethylol propane; nifedipine; drug delivery; graft copolymer

INTRODUCTION

PEGylated biopolymers such as polyesters, polyanhydrides, and polyurethanes (PUs) have tremendous applications as drug delivery matrices because of their good stability, low surface tension, and excellent blood compatibility. Implantable biomedical devices made of such polymeric materials, for use as blood-contacting intravascular catheters, have been extensively utilized for the interventional treatments in clinical practice. However, the surfaces of these devices may promote *in situ* blood coagulation, microbial infections, and consequent inflammatory reactions.[1,2] It is believed that these iatrogenic effects are likely to be mediated by the adsorbed host proteins on the device surfaces.[3,4] It is also widely accepted that albumin-coated surfaces can minimize such harmful effects.[5,6] Thus, a series of novel surface-modifying additives have been designed to develop surfaces that would selectively bind the host albumin. PUs are relatively interesting because of their widespread characteristics related to the nature of the monomers used.[7–10] Especially, poly (ether urethanes) have been widely studied due to their excellent physical properties such as flexibility, glass transition temperature (T_g), and degradation characteristics in addition to resistance for infectiousness and superior compatibility.[11–13]

Polyethylene oxide (PEO) is a well-known and useful hydrophilic biomaterial, which under aqueous physiological conditions, has a high kinetic chain mobility and large thermodynamic steric volume,[14] leading to the repulsion of almost all kinds of foreign adherence and adsorption. A major problem to achieve an effective drug-targeting polymer to the specific sites within the body is the sequestration of intravenously administered colloidal carriers by cells of the mononuclear phagocytic system (MPS). However, the MPS uptake and consequent organ deposition can be avoided by sterically stabilizing

This article is CEPS communication no. 157.
Correspondence to: T. M. Aminabhavi (aminabhavi@yahoo.com).
Contract grant sponsor: University Grants Commission, New Delhi, India (for major financial support to establish the Center of Excellence in Polymer Science); contract grant number: F1-41/2001/CPP-II.

the colloidal particles with a layer of PEO chains on the particle surface.[15,16] In the previous literature,[17,18] PUs were essentially used to prepare microparticles having an average size ranging from 10 to 200 μm. PUs represent a major class of synthetic elastomers that have been evaluated for a variety of medical implants, particularly for long-term implants.[19,20] They have shown excellent mechanical properties and good biocompatibility; hence, they were used in the fabrication of medical implants such as cardiac pace makers and vascular grafts. Recent developments in siloxane-based PUs, which have the greater *in vivo* stability than the conventional polyetherurethanes [e.g., poly(tetramethylene oxide)-based], provided ample opportunities for the development of a range of medical implants for chronic disease applications.[21] PUs can also be designed to have chemical linkages that are degradable in the biological environment, since PUs can be tailored to exhibit a broad range of mechanical properties with good biocompatibility.

Recently, there has been some interest to develop biodegradable PUs for biomedical applications such as scaffolds in tissue engineering.[22] However, the major problem has been the toxicity of degradation products, particularly those derived from diisocyanate component. For example, degradation products of PUs based on diisocyanates such as 4,4′-methylenediphenyl diisocyanate (MDI) and toluene diisocyanate (TDI) are toxic.[23,24] Accordingly, in designing the degradable PUs, diisocyanates such as lysine diisocyanate (LDI) (2,6-diisocyanatohexanoate) and other aliphatic diisocyanates like hexamethylene diisocyanate (HDI), 1,1-methylenebis(dicyclohexyl-4,4-diisocyanate) (^{12}H-MDI), and 1,4- butanediisocyanate have been widely used. Artificial organs, vascular grafts, intravascular stents, and various prosthetic devices cannot be introduced into the body if their surface is thrombogenic. It is generally believed that thrombus formation is initiated by the adsorption of proteins from plasma, followed by platelet adhesion and activation. It seems that antithrombogenic characteristics may be induced by the hydrophilic/hydrophobic microdomains on the surface.

Several PUs known under the commercial names of Pellethanes and Biomers are available for biomedical applications. The nonthrombogenic characteristics of polymeric objects can be enhanced by grafting *N*-alkyl acrylamides onto their surface by coating it or grafting onto PEO, which is relatively unreactive towards plasma proteins and cells.[25–27] The surface modification approach has also been used to further improve the hemocompatibility of PU block copolymers. The grafting of acrylic acid onto poly(etherurethane-urea), synthesized from (1.3 : 1 : 1) MDI : poly (tetramethylene glycol) (M_w = 1000) : ethylene diamine as the chain extender, activated by treatment with oxygen plasma enabled the subsequent attachment of heparin. As a result of such treatment, the activation of plasma proteins and platelets has been effectively suppressed and the material with good *in vitro* blood compatibility has been obtained.[28] It had been noted several years ago that grafting of PEO onto the surface of biomer improves its blood compatibility.[29]

Realizing their importance, in the present study, two monomers viz. lauric acid-trimethylol propane (LA-TMP) and mPEG-TMP were prepared and used as diols to prepare the PEGylated PUs. The polymers prepared were further developed as microspheres for the controlled release (CR) of a model antihypertensive drug viz. nifedipine (NFD). The *in vitro* release studies have been performed in 7.4-pH phosphate buffer at 37°C. The kinetics of drug release was evaluated using an empirical equation. The prepared microspheres as well as the drug-loaded microspheres were characterized using different techniques to understand the formation of microparticles, surface morphology, as well as their chemical interaction with drug and their sizes.

EXPERIMENTAL

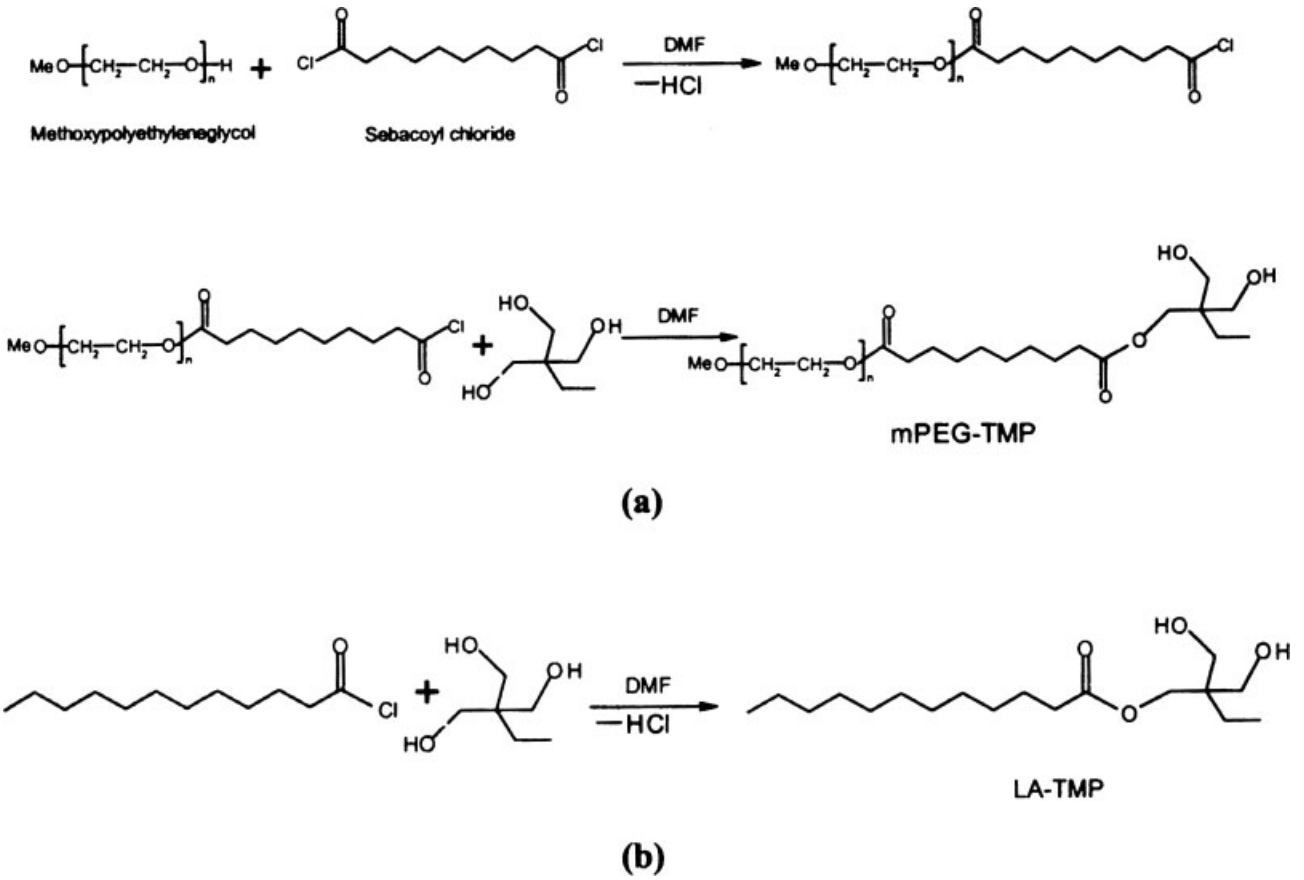
Materials

Analytical grade diethylene glycol (DEG), *N*,*N*-dimethyl formamide (DMF), and dichloromethane were obtained from S.D. Fine Chemicals, Mumbai, India. DEG and DMF were dried over 4-Å molecular sieves prior to use. NFD was procured from Loba Chemicals, Mumbai, India. 4,4′-Methylenebis(cyclohexylisocyanate) (^{12}H-MDI), dibutyl tin dilaurate, methoxypolyethyleneglycol (mPEG 2000),[30] trimethylol propane (TMP), sebacoyl chloride, 1,4-butanediol, and lauroyl chloride were all purchased from Aldrich Chemical Company, Milwaukee, WI.

Methods

Synthesis of mPEG-TMP

Sebacoyl chloride was taken in a dry round bottom flask fitted with calcium chloride guard tube and addition funnel. To this, mPEG and triethyl amine dissolved in DMF in 1 : 1 ratio with respect to sebacoyl chloride were added dropwise under constant magnetic stirring and the mixture was further stirred for overnight. The obtained —COCl terminated mPEG was filtered to remove the triethylamine chloride salt. TMP was taken into the round bottom flask along with triethylamine. To this mixture, —COCl terminated mPEG was added dropwise under magnetic stirring for overnight. The reaction mixture was filtered, the DMF was removed under high vacuum, and the product was stored in a desic-



Scheme 1 Synthesis of (a) mPEG-TMP and (b) LA-TMP.

cator until further use. The chemical reaction leading to the preparation of mPEG-TMP is shown in Scheme 1(a).

Synthesis of LA-TMP

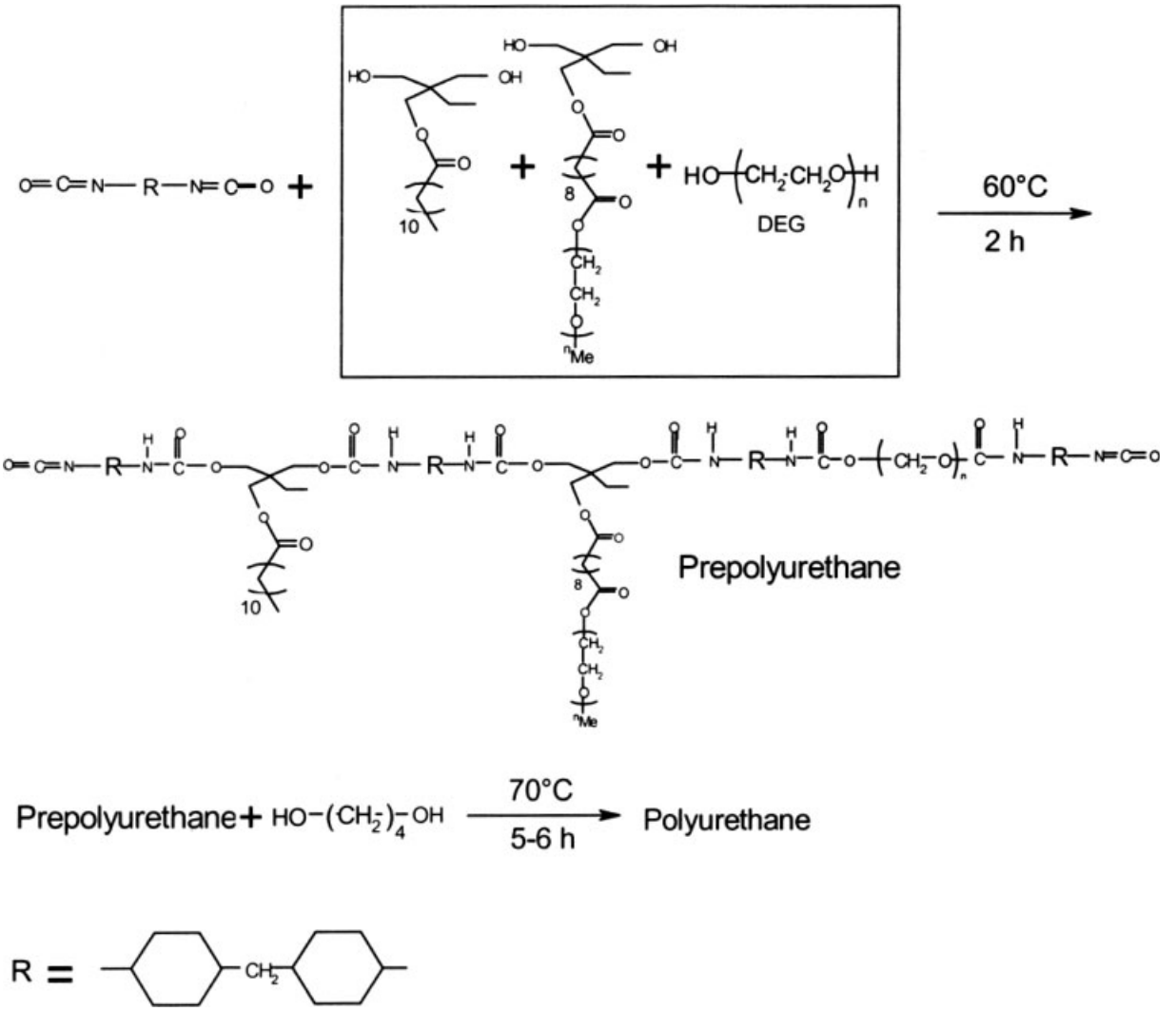
TMP and triethyl amine (1 : 1.1) were taken in a dry round bottom flask containing DMF, equipped with a guard tube and addition funnel. Lauroyl chloride was added dropwise from the addition funnel under magnetic stirring. After complete addition of acid chloride for about half an hour, the salt of triethylamine was observed in the reaction mixture. The stirring was further continued for overnight, the reaction mixture was filtered, and the solvent from the filtrate was removed under high vacuum. The chemical reaction leading to the formation of LA-TMP is shown in Scheme 1(b).

Preparation of PU

Moderate molecular-weight block PUs were obtained by mixing two or more than two diols. Methoxy polyethylene glycol-TMP (0.005 mol), LA-TMP (0.005 mol), and DEG (0.01 mol) were dissolved in DMF taken in a 100-mL round bottom flask fitted with the addition funnel and a guard tube. Dibutyl tin dilaurate (0.02%) was added to it and stirred on a magnetic stirrer for about 10–15 min under nitrogen atmosphere. A 0.04 mol of ^{12}H-MDI was added dropwise to the above reaction mixture. The reaction mixture was stirred for 30 min and subsequently heated at 60°C for 2 h to get the isocyanate-terminated PU. The reaction mixture was cooled to ambient temperature and 1,4-butanediol (0.02 mol) was added to isocyanate-terminated PU as a chain extender. The mixture was again heated at 70°C for 5–6 h. After completion of the reaction, the mixture was cooled to room temperature, the product was precipitated in distilled water, and collected by filtration. The filtered product was dried in a vacuum oven at 60°C. Different PUs were prepared by varying the ratio of LA-TMP and mPEG-TMP. Reactions leading to the preparation of mPEG-TMP and LA-TMP as well as the formation of PUs are given in Schemes 1 and 2, respectively. Formulation codes and different ratios of the monomers used for PU preparation are given in Table I.

Preparation of NFD-loaded microspheres

Microspheres of mPEG-grafted PU containing hydrophobic NFD drug were prepared by solvent



Scheme 2 Synthesis of PUs from mPEG-TMP and LA-TMP.

evaporation technique. PU (100 mg) was dissolved in dichloromethane (4 mL), followed by adding NFD to the polymer (1 : 0.1) at appropriate weight ratio, and stirred at ambient temperature. The polymer/drug solution was added dropwise to a 2% PVA solution under constant stirring using a Eurostar high-speed stirrer (IKA Labortechnik, Germany) at 800 rpm rotor speed. The solution was further stirred for a period of about 20–30 min to achieve the complete evaporation of dichloromethane; the solution was then diluted with distilled water and microspheres were isolated using the tabletop centrifuge (Jouan, MR 23i, France). The PU microspheres were washed several times by fresh distilled water to remove the adhering substances such as dispersion stabilizers or nonencapsulated drugs.[31,32] The obtained microspheres were redispersed into deionized water and lyophilized by a freeze-dryer (Jouan, LP3, France) to obtain the completely dried microspheres.

Drug loading efficiency

Microspheres were dissolved in DCM and the amount of NFD entrapped was determined by UV spectrophotometer (Secomam, Anthelie, France) at the λ_{max} value of 238 nm. These data were collected in triplicate, but the average values were considered to calculate % drug loading and encapsulation effi-

TABLE I
Formulation Codes and Different Ratio of Monomers Used in PU Preparation

Formulation codes	mPEG-TMP (%)	LA-TMP (%)
PU-*g*-PEG-1	10	90
PU-*g*-PEG-2	20	80
PU-*g*-PEG-3	30	70
PU-*g*-PEG-4	40	60
PU-*g*-PEG-5	50	50

TABLE II
% Drug Loading and Drug Loading Efficiency of 10% NFD Loaded PUs

Formulation codes	Encapsulation efficiency (%)	Microsphere diameter (μm)
PU-*g*-mPEG-1	92	10–20
PU-*g*-mPEG-2	87	10–30
PU-*g*-mPEG-3	81	20–35
PU-*g*-mPEG-4	72	25–40
PU-*g*-mPEG-5	65	40–50

ciency. The NFD content entrapped into microspheres was calculated using the following equations:

$$\text{Actual drug loading (\%)} = \left(\frac{\text{Weight of drug in microspheres}}{\text{Weight of microspheres}}\right) \times 100 \quad (1)$$

$$\text{\% Encapsulation efficiency} = \left(\frac{\text{Actual drug loading}}{\text{Theoretical drug loading}}\right) \times 100 \quad (2)$$

Table II shows the results of amount of NFD loading and drug loading efficiency of PU.

In vitro drug release

Weighed amounts of drug-loaded microspheres (10 mg) were suspended in 100 mL of phosphate buffer, pH 7.4, and 0.1% (w/v) polysorbate-80 surfactant. The dissolution medium was stirred at the speed of 100 rpm and 37°C using the water bath with a shaker (Grant OLS200; Grant Instruments, Cambridge, UK). Aliquots of dissolution medium (3 mL) were withdrawn and filtered through 0.45-mm millipore filter at the predetermined time intervals. After appropriate dilution, the drug concentration was analyzed by UV spectrophotometer (Secomam) at the λ_{max} value of 238 nm. Dissolution medium was maintained at constant volume by replacing the samples with a fresh dissolution medium.

Gel permeation chromatography

Molecular weights of the synthesized PUs were determined by gel permeation chromatography (GPC) (Viscotek, Houston, TX) attached to a differential refractive index detector (VE 3580; Viscotek) by employing two columns (Viscotek gel, GMHH *R*-H). The flow rate of the mobile phase, viz. THF, was set to 1 mL/min; polystyrene standards were used for the calibration runs. Subsequently, the molecular weight of PUs was reported as the polystyrene equivalent molecular weight. The results of molecular weight and polydispersity index are given in Table III.

Fourier transform infrared spectra

Fourier transform infrared (FTIR) spectra of the polymers were determined using a Nicolet 5700 spectrophotometer (Milwaukee, WI) at the spectral range of 4000–400 cm^{-1}. Samples were crushed with KBr to get the pellets by applying a pressure of 600 kg/cm^2.

X-ray diffraction

X-ray diffraction (X-RD) studies were carried out on the drug-loaded microspheres and plain drug samples using a powder X-RD technique with a Philips model PW-1710 diffractometer (UK) attached to a digital graphical assembly and a computer with Cu-NF 25 KV/20-mA tube as the Cu Kα radiation source in the range 0°–50° of 2θ. These measurements were done at USIC, Shivaji University, Kolhapur, India.

Scanning electron microscopy

Scanning electron microscopy (SEM) images of the microspheres were recorded using Jeol JSM 6400 scanning electron microscope (Japan) at the required magnification. A thin film of 10-nm gold coating was done before subjecting the samples to SEM.

Particle size analyzer

Particle size was measured by a laser light scattering technique (Mastersizer 2000, Malvern, UK). The sizes of the completely dried microspheres of different formulations were measured using a dry sample adopter. The volume-mean diameter (*Vd*) was recorded and these results are included in Table II.

RESULTS AND DISCUSSION

Gel permeation chromatography

Upon characterizing the newly prepared PU, by GPC, we found that molecular weights of the PUs

TABLE III
Molecular Weight and Polydispersity Index of the Polymers by GPC

Polymer code	M_w	M_w/M_n
PU-*g*-mPEG-1	27000	1.37
PU-*g*-mPEG-2	32500	1.32
PU-*g*-mPEG-3	37200	1.38
PU-*g*-mPEG-4	40100	1.28
PU-*g*-mPEG-5	43500	1.40

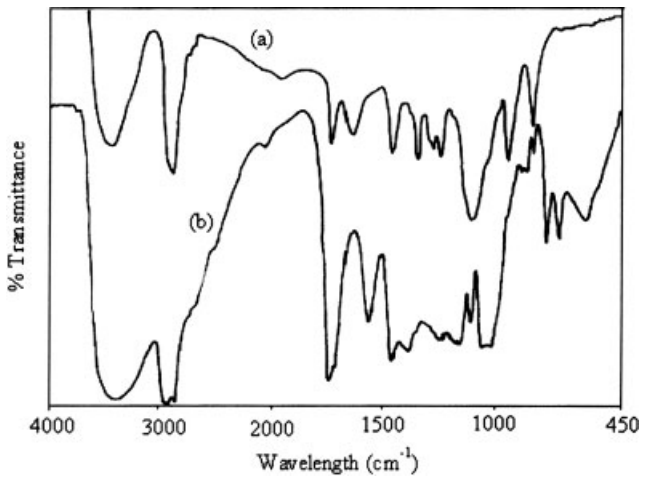


Figure 1 FTIR spectra of (a) mPEG-TMP and (b) LA-TMP.

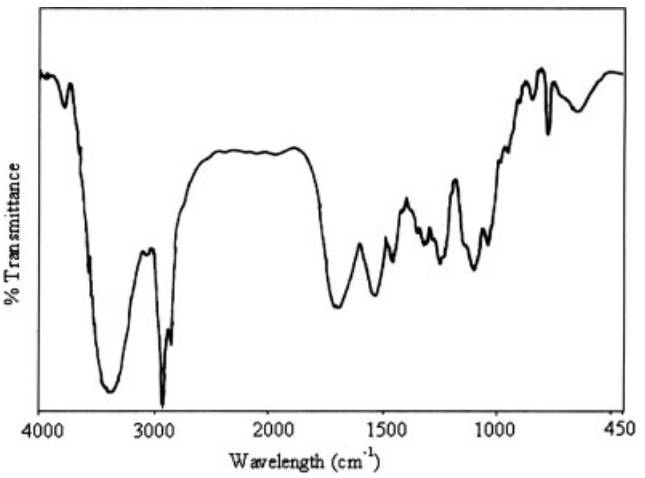


Figure 2 FTIR spectrum of PU prepared from 50% of mPEG-TMP and LA-TMP.

increased with increasing molar ratio of mPEG-TMP with respect to LA-TMP. Such an increase is due to the increase in the ratio of high molecular weight of mPEG (M_w = 2000)-TMP monomer present in the PU. The results on molecular weight and polydispersity index are shown in Table III. It is observed that with increasing molecular weights M_w of the grafted polymers, the polydispersity index also increased systematically. However, the variation of polydispersity index is not considerable realizing the wide variations in the molecular weight from 27,000 to 43,500 for PU-*g*-PEG-1 to PU-*g*-PEG-5 polymers. Thus, the method of preparing PUs used in this study produced somewhat uniformly distributed molecular segments in the prepared polymers.

FTIR spectra

Peak assignments for mPEG-TMP and LA-TMP

The characteristic peak of the ester linkage was seen around 1740 cm^{-1}, while the band around 3400 cm^{-1} confirms the presence of —OH group of the diol moiety. The band around 2800 cm^{-1} indicates the C—H stretching vibration. The absence of a peak around 1800 cm^{-1}, due to the presence of an acid chloride, indicates the absence of acid chloride in the reaction mixture.

Peak assignments for PUs prepared from mPEG-TMP and LA-TMP

The absence of a peak due to isocyanate around 2260 cm^{-1} indicates the complete reaction between diol and diisocyanate moieties, resulting in the formation of a urethane linkage. However, a broad band located at 3345 cm^{-1} is due to N—H stretching of the urethane linkage. The characteristic peak of carbonyl group of urethane linkage (—NHCOO) appeared at 1708 cm^{-1}, while the peak due to C—N stretching vibration is located at 1530 cm^{-1}. The aliphatic C—H stretching vibrations are seen around 2850 cm^{-1}. Overall, the FTIR data displayed in Figures 1 and 2 confirm the formation of structures and support the proposed reaction schemes.

X-ray diffraction

Figure 3(a,b) displays, respectively, the distinct X-RD patterns of pure NFD and NFD-loaded PU. The peaks of interest for pure drug are observed at 2θ of 12°, 18°, 22°, and 26°, while those of the drug-loaded PUs have appeared around 2θ of 20° and 45°. The missing of peaks is seen around 2θ of 22° and 26°, while these peaks were obtained at 16° and 19°. The broad peaks obtained in drug-loaded microspheres

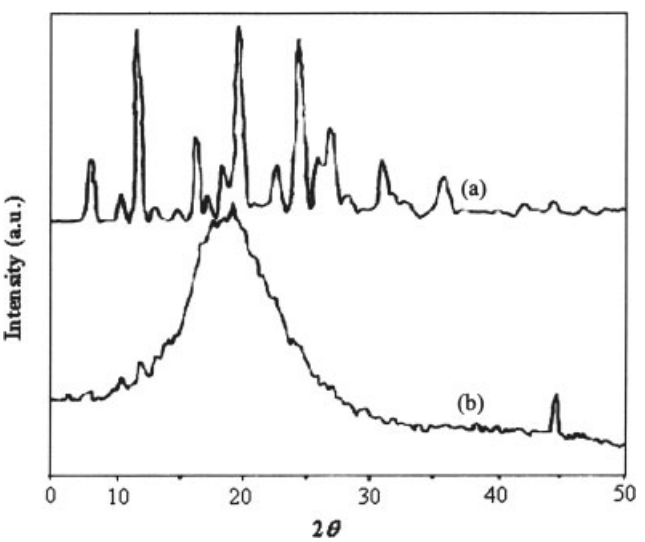


Figure 3 X-RD spectra of (a) pure NFD and (b) NFD-loaded PU microspheres.

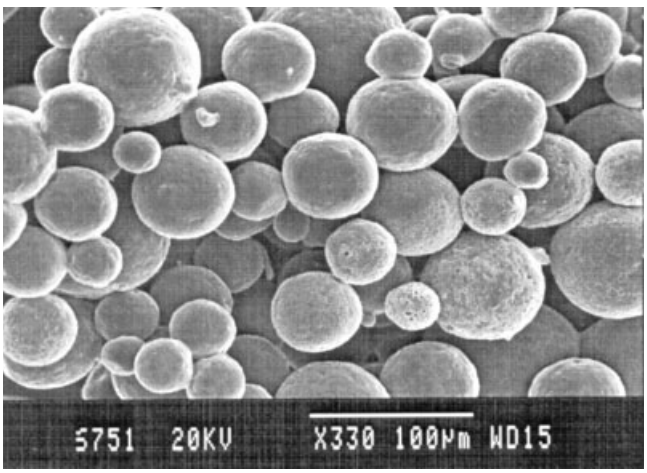


Figure 4 SEM picture of NFD-loaded group of microspheres.

indicate the amorphous nature of the drug in the polymer, since all the crystalline peaks of the drug are masked. This indicates the homogeneous mixing of drug particles of the designed PU matrices after encapsulation.

Scanning electron micrograph

The SEM micrograph of the drug-loaded PU-*g*-PEG-5 sample is shown in Figure 4. The micrograph indicates that the microspheres prepared using PU-*g*-PEG are spherical in shape, but some particles exhibit wrinkled surfaces. It may be noted that the mPEG grafted on prepared PUs is soluble in water, and hence, their SEM pictures show some porosity as evidenced by the presence of pores on the surface of the microspheres. This could be due to the presence of mPEG on the surface of microspheres during the production of microparticles from solution.

Particle size analysis

Particle size analysis of the microparticles as measured by laser-light scattering technique suggests an increasing trend of the sizes with increasing amount of mPEG in the PU, particularly PU-*g*-mPEG-1, PU-*g*-mPEG-2, PU-*g*-mPEG-3, PU-*g*-mPEG-4, and PU-*g*-mPEG-5 polymers. The size of microspheres increased from 10 to 50 μm. Such an increase in size with respect to increase in mPEG-TMP segments in PUs is because of the high viscosity of PU solution prepared in DCM. The increase of mPEG-TMP segments with respect to LA-TMP of the derived PUs increased their molecular weights. Notice that increase in the size of microspheres was also observed because of the bulk structure of mPEG molecule attached to TMP in the prepared PUs as well as high viscosity of PU solution with an increase in their molecular weights. The microparticles were prepared at a constant stirring fixed speed of about 800 rpm in solution containing 100 mg of the grafted PU in 4 mL of DCM.

Drug loading efficiency

Results of % drug loading and % encapsulation efficiency for different formulations are presented in Table II. In all the formulations developed, a fixed amount of NFD (10 wt %) was used during initial loading into the PU matrix. UV spectral results suggest that % NFD loading was decreased as a result of increase in the amount of mPEG-TMP in PUs. The loadings of NFD in all the PU-*g*-mPEG-1, PU-*g*-mPEG-2, PU-*g*-mPEG-3, PU-*g*-mPEG-4, and PU-*g*-mPEG-5 matrices are 9.2, 8.7, 8.1, 7.2, and 6.5%, respectively. However, the % encapsulation efficiency decreased from 92 to 65 with an increasing amount of molar ratio of mPEG-TMP with respect to LA-TMP. The observed decrease in % encapsulation efficiency with increasing amount of mPEG of the derived matrices is quite systematic. For instance, when the microspheres were prepared from PU-*g*-PEG-1, the encapsulation efficiency was 92%, while that with 20% of mPEG-TMP, i.e., PU-*g*-mPEG-2 it was 87%. For 30, 40, and 50% mPEG-TMP containing PUs, the encapsulation efficiencies were 81, 72, and 65%, respectively. These data suggest a significant reduction in % drug loading as well as % encapsulation efficiency that are attributed to the hydrophilic nature of mPEG; however, NFD being hydrophobic would play a major role in decreasing the % encapsulation efficiencies of the developed matrices. Notice that the size of the microparticles tends to increase systematically with increasing amount of mPEG of the grafted PUs. This is obvious because of the increased chain dimensions as noticed by the molecular weight data given in Table III.

In vitro drug release studies

In vitro release characteristics of mPEG and LA grafted PUs were evaluated for the CR of NFD in the studied medium. The plots of % cumulative release versus time for NFD-loaded PU microspheres are presented in Figure 5 for different formulations. From the release profiles, it can be seen that no burst effects are observed in all matrices. However, only 4, 7, 9, and 16% of NFD was released from PU-*g*-mPEG-1, PU-*g*-mPEG-2, PU-*g*-mPEG-3, and PU-*g*-mPEG-4, respectively, whereas the release was increased to 21% from the PU-*g*-mPEG-5 formulation during the first hour. The release studies were performed up to 83 h and it was observed that 69, 79, 86, 93, and 97% of NFD were released from the PUs prepared by varying mPEG-TMP (hydrophilic) and

LA-TMP (hydrophobic) segments, i.e., PU-*g*-mPEG-1, PU-*g*-mPEG-2, PU-*g*-mPEG-3, PU-*g*-mPEG-4, and PU-*g*-mPEG-5, respectively. Release rates were slowed down after about 50 h. Notice that faster release rates were observed for those formulations that contained the higher amount of mPEG-TMP and vice versa. This effect can be related to molecular chain dimension of the polymers as well as the size of microparticles prepared.

Drug release kinetics

In the pharmaceutics literature, the majority of published articles have analyzed the release data in terms of empirical relationships proposed by Higuchi and coworkers[33,34] and that of Ritger and Peppas.[35] Following this practice, we have also analyzed the release data using Higuchi equation given by:

$$\frac{M_t}{M_\infty} = kt^{0.5} \tag{3}$$

From the least squares fitting of the data, we have computed the values of k, a kinetic rate constant, which is independent of the geometrical and structural properties of the polymers. In the above equation, M_t is the amount of NFD released at time t and M_∞ is the amount of NFD released after a longer time. According to Ritger and Peppas,[35] the equation was slightly modified to include an exponential term n such that:

$$\frac{M_t}{M_\infty} = kt^n \tag{4}$$

Here, the values of the exponent n were calculated from the slope of the plots of ln (M_t/M_∞) versus ln t by the method of least squares at 95% confidential limit. These data along with n values for all the PUs loaded with different amounts of NFD are given in Table IV. It may be noted that if $n = 0.5$, then diffusion follows the Fickian mechanism, but if $0.5 < n < 1$, the anomalous transport is operative due to the possible matrix swelling.

In the present research, we found that the values of n lie between 0.7 and 1.29, indicating a shift from the anomalous to super Case-II transport of NFD through the PU matrices (see data presented in Table IV). However, these data along with the values of k showed a decline with a systematic increase in the size of microparticles. Smaller values of k indicate a prolonged release of NFD from the PU microspheres. The values of k decreased with an increasing amount of mPEG-TMP, which indicates the higher release rates of the drug-loaded matrices. Previous studies reported in the literature also suggested similar anomalies.[36–38]

TABLE IV
Release Kinetics Data for Drug Loaded PU Microspheres Using Higuchi and Power Law Equations

Formulation codes	Higuchi law		Power law	
	k	r^2	n	r^2
PU-*g*-mPEG-1	0.12	0.98	1.29	0.98
PU-*g*-mPEG-2	0.12	0.98	1.11	0.99
PU-*g*-mPEG-3	0.11	0.98	1.01	0.97
PU-*g*-mPEG-4	0.11	0.98	0.83	0.99
PU-*g*-mPEG-5	0.10	0.98	0.7	0.99

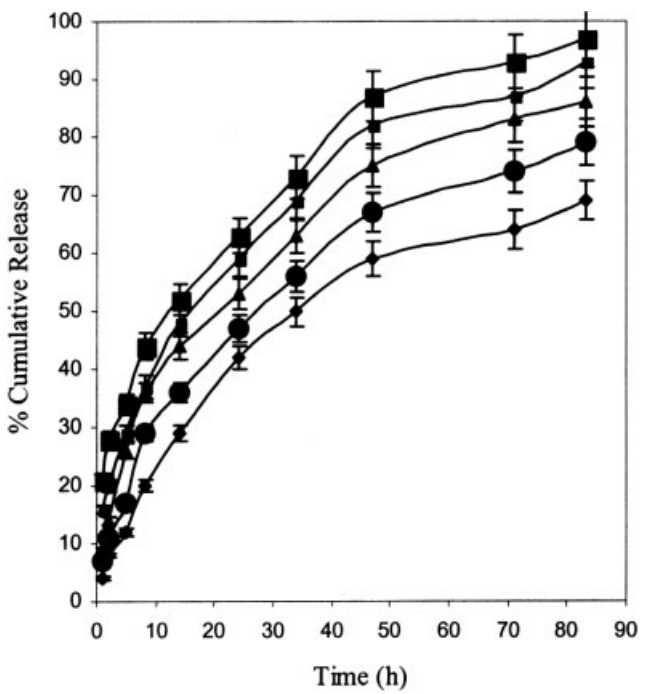


Figure 5 Drug release profiles of NFD from PU microspheres prepared from (a) 10% mPEG-TMP (◆), (b) 20% mPEG-TMP (●) (c) 30% mPEG-TMP (▲), (d) 40% mPEG-TMP (■) and (e) 50% mPEG-TMP (■) at 37°C.

CONCLUSIONS

The work reported here on the development of novel polymeric matrices based on the grafted PUs produced matrices that are useful in the CR of NFD, an antihypertensive drug, which is widely used in pharmaceutical industries for the treatment of heart ailments. The matrices formed were tailored with different ratios of the monomers and developed as microspheres for a successful loading of NFD drug. The release study showed that varying the ratio of mPEG-TMP and lauric acid-TMP in the matrices controlled the drug release. Hydrophobic and hydrophilic grafted PUs of this study have shown the unique advantages to release NFD in controlled

manner up to 80 h and the prepared microspheres are stable during the testing period. It is also demonstrated that a hydrophilic and lipophilic balance of the matrices can be achieved by varying the ratio of two different diols to obtain the suitable PU matrices for the release of a fast acting drug such as NFD. The polymers of this study were prepared by using the biocompatible LA monomer and aliphatic isocyanate like 4,4′-methylenebis(cyclohexylisocyanate). Thus, their use in CR applications can be exploited for a variety of other drugs. Research in this direction is in progress.

The authors thank Mr. S. B. Teli of Shivaji University, Kolhapur, India, for providing the X-RD and FTIR data reported in this article.

References

1. Lelah, M. D.; Cooper, S. L. Polyurethanes in Medicine; CRC Press: Boca Raton, FL, 1986; p 57.
2. Ikada, Y. Adv Polym Sci 1984, 57, 103.
3. Han, D. K.; Park, K. D.; Rug, G. H.; Kim, U. Y.; Min, B. G.; Kim, Y. H. J Biomed Mater Res 1996, 30, 23.
4. Aldenhoff, Y. B. J Biomed Mater Res 1995, 29, 917.
5. Pitt, W. G.; Cooper, S. L. J Biomed Mater Res 1988, 22, 359.
6. Pitt, W. G.; Grasel, T. G.; Cooper, S. L. Biomaterials 1988, 9, 36.
7. Boretos, J. W. Pure Appl Chem 1980, 52, 1851.
8. Sharma, K.; Knutson, K.; Kim, S. W. J Control Release 1988, 7, 197.
9. Szycher, M.; Poirier, V. L. Ind Eng Chem Prod Res Dev 1983, 22, 588.
10. Kohjiya, S.; Ikeda, Y.; Takesako, S.; Yamashita, S. React Polym 1991, 15, 165.
11. Langer, R. S.; Folkman, J. M. In Biomedical Polymers: Polymeric Materials and Pharmaceutics for Biomedical Use; Goldberg, E. P.; Nakajima, A., Eds.; Academic Press: New York, 1980; p 113.
12. Kohjiya, S.; Ikeda, Y. Nihon Gomu Kyokaishi 1989, 62, 357.
13. Lelah, M. D.; Lambercht, L. L.; Young, B. R.; Cooper, S. L. J Biomed Mater Res 1983, 17, 1.
14. Llanos, G. R.; Sefton, M. V. J Biomater Sci Polym Ed 1993, 4, 381.
15. Illum, L.; Davis, S. S. FEBS Lett 1984, 167, 79.
16. Illum, L.; Davis, S. S.; Muller, R. H.; Mak, E.; West, P. Life Sci 1987, 40, 367.
17. Hong, K.; Park, S. React Funct Polym 1999, 42, 193.
18. Frère, Y.; Danicher, L.; Gramain, P. Eur Polym J 1998, 34, 193.
19. Pinchuk, L. A. J Biomater Sci Polym Ed 1994, 6, 225.
20. Lamba, N. M. K.; Woodhouse, K. A.; Cooper, S. L. Polyurethanes in Biomedical Applications; CRC Press: New York, 1998; p 205.
21. Gunatillake, P. A.; Meijs, G. F.; McCarthy, S. J. In Biomedical Applications of Polyurethanes; Vermette, P.; Griesser, H. J.; Laroche, G.; Guidoin, R., Eds.; Landes Bioscience: Georgetown, 2001; p 160.
22. Zdrahala, R. J.; Zdrahala, I. J. J Biomater Appl 1999, 14, 67.
23. McGill, D. B.; Motto, J. D. New Engl J Med 1974, 291, 278.
24. Gogolewski, S.; Pennings, A. J. Makromol Chem Rapid Commun 1982, 3, 839.
25. Amiji, M.; Park, K. Polymers of Biological and Biomedical Significance (ACS Symposium Series 540); ACS: Washington, DC, 1994; p 135.
26. Loh, I. H.; Sheu, M. S.; Fischer, A. B. In Desk Reference on Functional Polymer Synthesis and Applications; Arshady, R., Ed.; ACS: Washington, DC, 1997; p 662.
27. Rihova, B. Adv Drug Deliv Rev 1996, 21, 157.
28. Kang, I. K.; Kwon, O. H.; Byun, K. H.; Kim, Y. H. J Mater Sci Mater Med 1996, 7, 135.
29. Zhang, X.; Burt, H. M. Pharm Res 1995, 12, S265.
30. Hua, Y. T.; Chao, D.; Hao, L.; Jingru, S.; Mingxiao, D.; Xuesi, C.; Xiabin, J. Biomaterials 2005, 26, 4209.
31. Sergio, F.; Hans, P. M.; Bruno, G. J Control Release 2005, 102, 313.
32. Passerini, N.; Craig, D. Q. J Control Release 2001, 73, 111.
33. Roseman, T. J.; Higuchi, W. I. J Pharm Sci 1970, 59, 353.
34. Otsuka, M.; Matsuda, Y.; Suwa, Y.; Fox, J. L.; Higuchi, W. I. J Pharm Sci 1994, 83, 611.
35. Ritger, P. L.; Peppas, N. A. J Control Release 1987, 5, 23.
36. Han, W. W. T.; Stevens, W. F. Drug Dev Ind Pharm 2004, 30, 397.
37. Gudasi, K. B.; Vadavi, R. S.; Shelke, N. B.; Sairam, M.; Aminabhavi, T. M. React Funct Polym 2006, 66, 1149.
38. Shelke, N. B.; Sairam, M.; Halligudi, S. B.; Aminabhavi, T. M. J Appl Polym Sci 2007, 103, 779.