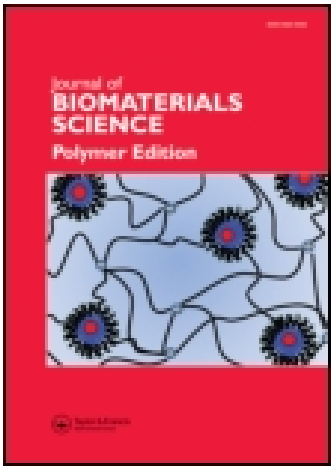
This article was downloaded by: [University of Chicago Library]
On: 10 October 2014, At: 11:27
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954
Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK




Journal of Biomaterials Science, Polymer Edition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/tbsp20

# Synthesis of 1-Octadecanol-Modified Water-Swelling Polyurethane Hydrogels as Vaginal Drug-Delivery Vehicle

Dechuang Yuan [a] , Caoyun Ju [b] , Song Ding [c] , Xiang Jing [d] & Can Zhang [e]

[a] Centre for Drug Discovery, China Pharmaceutical University, Nanjing 210009, P. R. China

[b] Centre for Drug Discovery, China Pharmaceutical University, Nanjing 210009, P. R. China

[c] Centre for Drug Discovery, China Pharmaceutical University, Nanjing 210009, P. R. China

[d] Centre for Drug Discovery, China Pharmaceutical University, Nanjing 210009, P. R. China

[e] Centre for Drug Discovery, China Pharmaceutical University, Nanjing 210009, P. R. China

Published online: 02 Apr 2012.

To cite this article: Dechuang Yuan , Caoyun Ju , Song Ding , Xiang Jing & Can Zhang (2010) Synthesis of 1-Octadecanol-Modified Water-Swelling Polyurethane Hydrogels as Vaginal Drug-Delivery Vehicle, Journal of Biomaterials Science, Polymer Edition, 21:4, 493-505, DOI: 10.1163/156856209X427032

To link to this article: http://dx.doi.org/10.1163/156856209X427032

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the

opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

Downloaded by [University of Chicago Library] at 11:27 10 October 2014

VSP

*Journal of Biomaterials Science 21 (2010) 493–505*

Journal of BIOMATERIALS SCIENCE
brill.nl/jbs

# Synthesis of 1-Octadecanol-Modified Water-Swelling Polyurethane Hydrogels as Vaginal Drug-Delivery Vehicle

**Dechuang Yuan, Caoyun Ju, Song Ding, Xiang Jing and Can Zhang** *

Centre for Drug Discovery, China Pharmaceutical University, Nanjing 210009, P. R. China

Received 24 November 2008; accepted 24 February 2009

Downloaded by [University of Chicago Library] at 11:27 10 October 2014

**Abstract**

The purpose of this work was to develop a novel polyurethane hydrogel system for sustained drug release, which could be used as a vaginal drug-delivery vehicle. The blank polyurethane hydrogels were synthesized by a polyol oligomeric, a diisocyanate and a triol (used as cross-linking agent). In order to improve the swelling ability of a polyurethane hydrogel, a small amount of 1-octadecanol was added. Additionally, the structure, mechanical properties and thermal properties of polymers were assessed by FT-IR, WAXD, DSC and mechanical tests. The results show that no more than 2.5 wt% of 1-octadecanol additives is sufficient to affect the release profile without changing the structure and mechanical properties of the polyurethane hydrogels obviously. Tinidazole was chosen as a model drug, the release data of drug from polyurethane hydrogels were fitted using the Ritger–Peppas equation and the result showed that it was non-Fickian diffusion, which means that the drug release was controlled by both swollen control and diffusion control. In conclusion, our work proves that the synthesized polyurethane hydrogel modified by 1-octadecanol may be a promising sustained release drug carrier.

© Koninklijke Brill NV, Leiden, 2010

**Keywords**

Poly(ethylene glycol), 1-octadecanol, hydrogel, polyurethane, vaginal delivery

## 1. Introduction

As a route for drug delivery the vagina has been used since ancient times. In recent years, due to its ability to by-pass first the metabolism, with ease of administration and high permeability for drug molecules overweighting other conventional drug delivery [1], the vaginal route has been rediscovered as a potential route for systemic delivery of peptides and other therapeutically important macromolecules. Among the synthetic hydrogels, the commonly used vaginal-controlled drug-release matrix, the hydrophilic polymer networks that may imbibe large amounts of

* To whom correspondence should be addressed. Tel.: (86-25) 853-33041; Fax: (86-25) 853-33041; e-mail: zhangcan@cpu.edu.cn

© Koninklijke Brill NV, Leiden, 2010 DOI:10.1163/156856209X427032

water or biological fluids in their swelling structure and exhibit a semi-solid morphology offer an effective and convenient way [2, 3].

Polyurethane (PU) hydrogels have great potential in biomedical and biotechnological applications and, therefore, have received extensive research and attention in the past years. The work done by Mequanint *et al*. [4] on the synthesis of cross-link polyurethane-block-poly(glycerol methacrylate) hydrogels for protein drug delivery is an example. A poly(ethylene glycol)-based polyurethane hydrogel was used as the matrix of a commercially available vaginal insert formulation, Cervidil®, containing dinoprostone for the initiation or enhancement of cervical ripening in women at or after term with a singleton pregnancy and a cephalic presentation [5].

With the goal of reducing drug diffusion during the early stages of release and achieving a controlled drug release, multitudes of drug release strategies were designed. Morimoto *et al*. modified the surface of segmented polyurethanes with 2-methacryloyloxyethyl phosphorylcholine (MPC) by forming a semi-interpenetrating polymer network [6]. Glutaraldehyde was used by Brazel's research group to modify poly(vinyl alcohol) hydrogels [7] and poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogels [8] through surface cross-linking. In addition, surface extraction, one of the simplest physical techniques, has been effectively used in several studies [7, 9], given the desorption of release of drugs that have been absorbed or trapped on the surface of the device. However, a simple method to regulate the matrix's drug diffusion in a wide range while keeping its physical properties is seldom reported.

In order to improve the drug-release profiles of PU hydrogels without affecting their cross-link ratio noticeably, in most cases, small amounts of hydrophobic reactive additives were incorporated during the synthetic process. Kurt and Wynne grafted 3-(2,2,2-trifluoroethoxymethyl)-3-methyloxetane, a hydrophobic material which was used as side-chain to the polymers [10], since the fluorinated side-chain can move to the surface of the polyurethanes during preparation. This method presents some advantages: (1) the incorporated modification results in additional functional groups on the surface whose reactive sites are insufficient; (2) it would provide an additional way to modify polyurethane hydrogel in controlled release drug delivery.

In this study, the blank PU hydrogels were normally synthesized from MDI as the diisocyanate, PEG 6000 as the diol and TMP as the chain-extending agent. 1-octadecanol was simply introduced as the hydrophobic additive affecting the hydrogels' swelling rate and equilibrium swelling ratio during swelling. Additionally, Tinidazole was chosen as the model drug and as the drug release for experiments *in vitro* were also conducted to evaluate the drug release behavior of the hydrogels. In sum, the major objective of this work is to evaluate the influence of the drug release and the characteristics of the PU hydrogels carried by the addition of 1-octadecanol. Other factors such as the ratio of soft segments and hard segments, the degree of phase separated of the polymer, and the molecular weight of the PEG could also affect the drug-delivery profiles. These will be discussed in further studies.

Downloaded by [University of Chicago Library] at 11:27 10 October 2014

## 2. Materials and Methods

### 2.1. Materials

Poly(ethylene glycol) (PEG, $M_n = 6000$, from Xilong Chemical, P. R. China), 4,4′-methylenebisphenyl diisocyanate (MDI, from Wanhua Chemical Reagent, P. R. China), trimethylolpropane (TMP, from Sino Pharm Chemical Reagent, P. R. China) as a cross-linking agent for the PU hydrogels, 1-octadecanol (Sino Pharm Chemical Reagent) as a hydrophobic additive and tinidazole (Zhuhai Vital Pharm, P. R. China) were used.

### 2.2. Polyurethane Synthesis

Blank PU hydrogels were synthesized using the following method. PEG 6000 (30 g) and TMP (0.30 g) were dried at 120°C for 8 h under vacuum whilst bubbling dry nitrogen through the melt in order to assist removal of water, and then MDI (3.0 g) was added to the mixture of glycols. The whole mixture was briefly stirred for 1 min and then degassed for 2 min, then pouring it into a preheated mould for curing, which was heated in an oven at 100°C for 16 h.

For the PU hydrogels containing 1-octadecanol, the same synthesis was employed. 1-octadecanol was incorporated with PEG before vacuum drying. The amount of 1-octadecanol additives is shown in Table 1.

### 2.3. Sample Preparation

The PU mould was cut away to give a long cylindric piece 6 mm × 15 mm in dimension and 0.12 mm in thickness. The small cylinders were treated by swelling them in a 7:3 (v/v) ethanol/water mixture for 48 h at ambient temperature, which were used to extract the bulk of water extractable fraction contained in PUs, and then dried under vacuum at 25°C.

**Table 1.**
Chemical composition of polyurethane hydrogels

| Polyurethane | PEG 6k (g) | TMP (g) | MDI (g) | 1-Octadecanol (g) | 1-Octadecanol (%) |
|---|---|---|---|---|---|
| PU0 | 30 | 0.30 | 3.00 | 0 | 0 |
| PU0.5 | 30 | 0.30 | 3.00 | 0.17 | 0.5 |
| PU1 | 30 | 0.30 | 3.00 | 0.33 | 1 |
| PU2 | 30 | 0.30 | 3.00 | 0.66 | 2 |
| PU2.5 | 30 | 0.30 | 3.00 | 0.83 | 2.5 |
| PU3 | 30 | 0.30 | 3.00 | 0.99 | 3 |
| PU4 | 30 | 0.30 | 3.00 | 1.33 | 4 |
| PU5 | 30 | 0.30 | 3.00 | 1.67 | 5 |

The number in the sample code denotes the wt% 1-octadecanol of the PU, the wt% 1-octadecanol is calculated as the wt% of 1-octadecanol per basic material weight.

Downloaded by [University of Chicago Library] at 11:27 10 October 2014

### 2.4. FT-IR Spectroscopy

IR spectra of the samples was recorded by a Fourier transform IR (FT-IR) spectrometer (370DTGS, Nicolet-Avatar, USA), the samples were swollen in water for 24 h at ambient temperature to make them fragile, mixed with potassium bromide with a mortar. Then, the mixture was dried under a infrared lamp before being made into laminate.

### 2.5. Differential Scanning Calorimetry (DSC)

The soft segment glass transition temperature ($T_g$) and the hard segment melting temperature of the PU were determined by DSC using a TA Instruments (1Pyris, Perkin-Elmer, USA). The DSC procedure was described as follows: the samples were heated at a ramp rate of 10°C/min from −20°C to 160°C to erase thermal history, held for 3 min at 160°C, cooled down to −20°C at a cooling rate of 10°C/min and held for 1 min at −20°C, then heated again to 160°C at a heating rate of 10°C/min.

### 2.6. Wide-Angle X-Ray Diffraction (WAXD)

WAXD data were collected using a Bruker D8 (Bruker, Karlsruhe, Germany), Cu $K_\alpha$ radiation with a nickel filter and a zero-background sample cell were used, operated under 40 kV and 30 mA. All samples were measured in the continuous scan mode at 8–35° ($2\theta$) with a scanning rate of 0.02° ($2\theta$)/s.

### 2.7. Mechanical Tests

Tensile properties were investigated by using a universal testing machine (4466Instron, CSI, USA) with a 500 N load cell at a cross-head velocity of 500 mm/min until failure. Tear strength were also investigated by using the machine with a 500 N load cell at a cross-head velocity at 200 mm/min until failure. Ultimate tensile strength, elongation, Young's modulus and tear strength were calculated from the collected force *versus* displacement data.

### 2.8. Swelling Characterization Study

Swelling characteristics were evaluated by following methods: each sample was weighed and then placed in 50 ml deionized water in a 100 ml beaker at 37°C. The dynamic swelling ratios were calculated by weight increase of the swelling samples and initial dried samples according to the following equation [11, 12]:

$$\text{Swelling } (\%) = \left( \frac{W_t - W_i}{W_i} \right) \times 100, \tag{1}$$

where $W_t$ and $W_i$ are the weight of the sample in the swelling condition at time $t$ and dry condition, respectively.

The equilibrium swelling ratios were calculated according to the following equation [8]:

$$q = \frac{W_e}{W_i}, \tag{2}$$

Downloaded by [University of Chicago Library] at 11:27 10 October 2014

where $W_e$ and $W_i$ are the weight of sample in the equilibrium swelling and dry conditions, respectively. Three samples of each PU were measured to obtain the mean swelling ratio.

### 2.9. In Vitro *Drug-Release Measurement*

The samples were immersed in the tinidazole (3 mg/ml in 7:3 (v/v) acetone/water), and the samples were allowed to proceed at ambient temperature for 48 h. The loading amount was determined by weight change after vacuum drying, according to the equation: loading weight $= W_l - W_i$, where $W_l$ is the weight of loaded sample, and $W_i$ the weight of the polymer sample.

Drug release of samples containing tinidazole was measured in a 1200 ml beaker containing 900 ml sodium acetate-acetic acid buffer (pH 3.5) at 37°C. Stirring was performed by a mechanical stirrer at 100 rpm. Samples of 2 ml were taken from the dissolution medium after 30, 60, 90, 120, 240 and 360 min. After sampling, 2 ml fresh solvent was added. The concentration of tinidazole was measured by HPLC using a C18 column (250 mm × 4.6 mm, Dikma Technologies) operated at room temperature. The mobile phase consisted of methanol/water/glacial acetic acid 50:50:0.1 (v/v/v); the flow rate was set to 1 ml/min, wavelength 310 nm. The chromatographic apparatus consisted of a 1050 pump (Hewlett Packard) and an 1100 variable wavelength UV detector (Agilent Technologies).

The release data of drug from polyurethane hydrogels were fitted using the Ritger–Peppas equation (equation (3)) in order to propose the possible release mechanism.

$$\ln\left(\frac{M_t}{M_\infty}\right) = n \ln t + \ln k, \tag{3}$$

where $M_t$ corresponds to the amount of drug released at time $t$; $M_\infty$ is the total amount of drug that must be released at infinite time; $k$ is a release constant related to the structure and geometric properties of the dosage form; $n$ is the release exponent indicating the type of drug-release mechanism.

## 3. Results and Discussion

### 3.1. *Synthesis of Polyurethanes*

Generally, the synthesis of PUs is performed by a one-shot technique [13] with very efficient mixing of all the raw materials, including polyol, chain extender and isocyanate, in one step during a short time.

In this study, the polymerization based on PEG 6000, MDI and TMP in one pot afforded PUs, and 1-octadecanol incorporated in the gel plays a role in regulating the rate of drug release.

It was found that PU4 and PU5 were too brittle to keep their lamellar appearance. This phenomenon can be explained by the role of 1-octadecanol, the mono-functional group reagent which is able to terminate the polymerization and,

Downloaded by [University of Chicago Library] at 11:27 10 October 2014

Downloaded by [University of Chicago Library] at 11:27 10 October 2014

therefore, the polymerization cannot react very well if more than a certain content, which in this study is 2.5 wt%, of 1-octadecanol is added.

The chemical composition and hard segment content of the hydrogels are shown in Table 1. The composition of PEG, MDI, and TMP were kept constant, and then the amount of 1-octadecanol was varied to obtain different polyurethanes. FT-IR analysis demonstrated the urethane formation [14] during polymer synthesis. The absence of a NCO peak at 2285–2240 $cm^{-1}$ implies that there was a negligible amount of free isocyanate group, indicating that the reaction was complete [14, 15], and their urethane structure was demonstrated by absorption bands at around 3450 $cm^{-1}$ (N–H stretching), 1540 $cm^{-1}$ (C–N stretching, combined with N–H out-of-plane bending), 1725 $cm^{-1}$ (C=O stretching) and 1115 $cm^{-1}$ (asymmetric C–O–C stretching). A small absorption band at around 1644 $cm^{-1}$ was due to the formation of urea linkages, which may be the reaction of some of the unreacted isocyanides with the atmospheric moisture while curing as a side-reaction.

### *3.2. Sample Preparation*

During the sample preparation, it was typically found that a cylinder of original weight of 0.45 g reduced to a weight of 0.33 g after going through the swelling and drying cycle. It was due to that some water or ethanol extractable fractions were extracted during the swelling process. The re-dried hydrogels were retained the original appearance except PU3. Ruptures were observed on the surface of PU3, because that the polymerization could not react completely due to the amount of 1-octadecanol additions. Thus, PU3 will not be discussed in the following sections.

### *3.3. Structural Characterization of Polyurethanes*

FT-IR spectroscopy gives useful qualitative information about the molecular structure of the PUs [16]. They were used to investigate the structural differences in hard and soft segments of synthesized polyurethanes with various 1-octadecanol fractions. Almost all the infrared research on polyurethanes has focused on two principal vibrational regions: the N–H stretching vibration (3200–3500 $cm^{-1}$) and the carbonyl C=O stretching vibration amide I region (1700–1730 $cm^{-1}$) [17, 18]. Polyurethanes are capable of forming several kinds of hydrogen bonds due to the presence of donor N–H group and a C=O acceptor group in the urethane linkage [19]. Therefore, hard segment–soft segment hydrogen bonding can exist. These bands have been widely used to characterize, at least semi-quantitatively, the hydrogen bonding state of the polymer [15]. It is well-known that in hydrogen-bonded urethane N–H and C=O bands appear at lower wave-numbers than those in free ones.

Figure 1 shows the FT-IR spectra of the C=O stretching vibration region for PEG-based polyurethanes. The broad band between 1750 and 1670 $cm^{-1}$ is attributable to associated and non-associated C=O urethane groups. Analysis of this stretching vibration for the PU0 indicates that there is a band at approx. 1725 $cm^{-1}$,

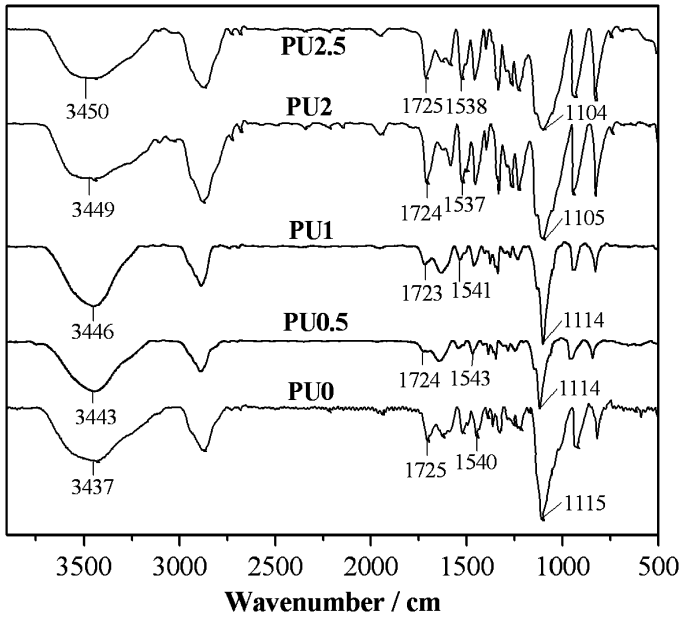



**Figure 1.** FT-IR spectra of the polyurethane hydrogels.

attributable to free C=O urethane groups, and a small shoulder at about 1700 $cm^{-1}$, due to the hydrogen-bonded C=O urethane [20]. The intensity of the bands attributed to free and hydrogen-bonded urethane carbonyls is similar with the addition of a small amounts of 1-octadecanol, which suggest that there is no visible difference among the polymers in structure. In the amine region, the broad band ascribed to N–H stretching shifts slightly to a higher wave-number with the addition of 1-octadecanol, indicating a decrease in the degree of association [13, 15]. The difference in the state of molecular aggregation of polyurethanes is further confirmed by DSC.

The addition of 1-octaedcanol cannot confirm its presence in the PUs according to the FT-IR spectroscopy. However, at the stage of equilibrium swelling, as it is shows in Fig. 2, the transparent swelling hydrogel gradually turned opaque with the increase of 1-octaedcanol additions. It is due to the existence of hydrophobic blocks. The result suggests that the addition of 1-octadecanol is grafted into the polymers successfully.

### *3.4. DSC Analysis*

Thermal analysis of the polymers obtained was performed to provide insights into the morphological structure of the material [21] to examine whether the structure of polyurethanes were affected by addition of the 1-octadecanol. Figure 3 shows the DSC curves of the polymers, and the data of their melting temperature and enthalpy are summarized in Table 2. Soft segments form a crystalline structure in the segmented polyurethane due to their long chain length and structure order [22].

Downloaded by [University of Chicago Library] at 11:27 10 October 2014

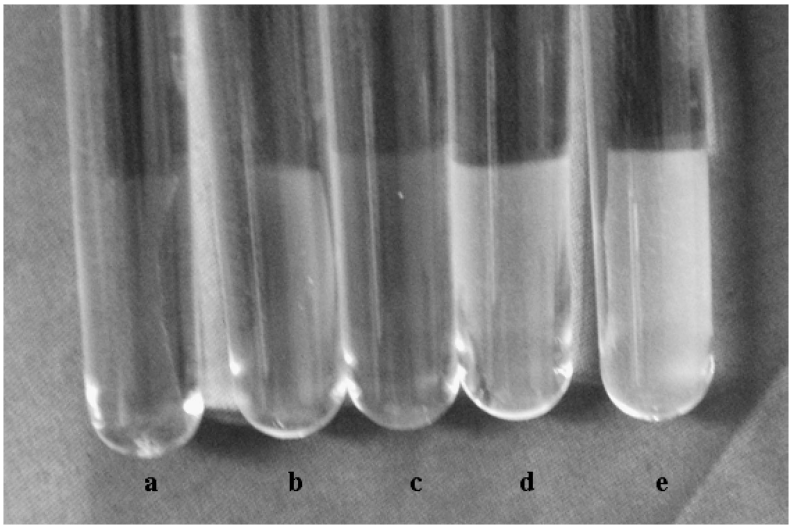



**Figure 2.** Images of equilibrium swelling samples: (a) PU0; (b) PU0.5; (c) PU1; (d) PU2; (e) PU2.5.

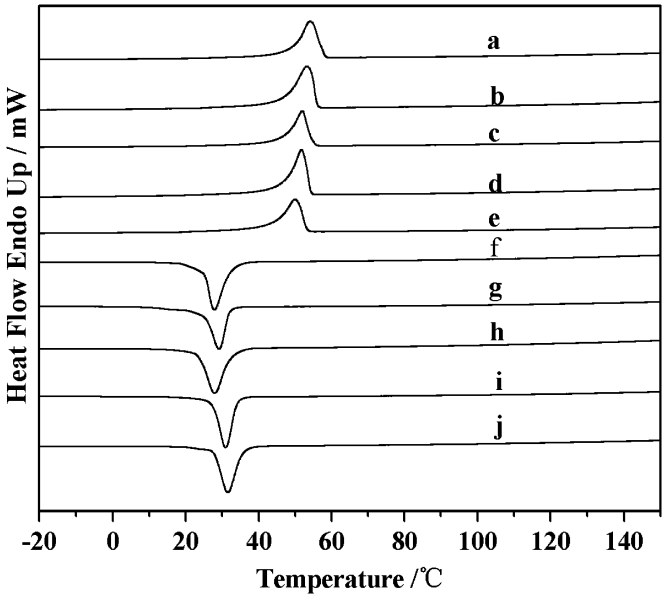



**Figure 3.** DSC curves of samples: (a) second heating cycle of PU0; (b) second heating cycle of PU0.5; (c) second heating cycle of PU1; (d) second heating cycle of PU2; (e) second heating cycle of PU2.5; (f) cooling cycle of PU2.5; (g) cooling cycle of PU2; (h) cooling cycle of PU1; (i) cooling cycle of PU0.5; (j) cooling cycle of PU0.

PEG 6000 is used as soft segment, which has a lower crystalline temperature in polymers. None of the DSC profiles indicates the existence of one or more glass transitions. This may be due to the glass transition falling out of the range of the

Downloaded by [University of Chicago Library] at 11:27 10 October 2014

**Table 2.**
Transition temperature and transition enthalpy of PUs

| Sample | $\Delta H$ (J/g) | | Tr (°C) | |
|---|---|---|---|---|
| | Heating cycle | Cooling cycle | Heating cycle | Cooling cycle |
| PU0 | 93.24 | 91.96 | 53.92 | 35.53 |
| PU0.5 | 86.42 | 83.82 | 52.61 | 33.63 |
| PU1 | 88.41 | 86.35 | 51.82 | 27.99 |
| PU2 | 86.57 | 84.93 | 51.84 | 32.29 |
| PU2.5 | 81.88 | 78.98 | 49.68 | 31.94 |

Tr — Peak transition temperature of samples; $\Delta H$ — phase transition enthalpy of samples.

Downloaded by [University of Chicago Library] at 11:27 10 October 2014

DSC experiment [23]. There is a melting peak at about 54°C in the heating scanning DSC curve of PU0 and the latent heat of fusion is 93.24 J/g, while in the heating scanning curve of samples with the addition of 1-octadecanol, shown in Fig. 3b–3e, the melting peaks and the enthalpy all decreased differently. Figure 3f–3j shows the cooling DSC curves of the polymers. They show that similar quantities of heat are released. It can be concluded that the addition of 1-octadecanol can decrease the crystallization temperature of polyurethanes. However, DSC offers limited information regarding the crystalline of polymer.

### *3.5. WAXD Analysis*

In order to obtain more information about the crystallization state of the copolymers, a WAXD study of the PUs was carried out. Figure 4 shows the WAXD patterns of the blank polyurethane and the modified ones. It has obviously showed that five samples had similar diffraction curves on which the diffraction angle (at $2\theta = 19.2°$ and 23.5°) and crystal plane distance are nearly the same, which means that they have nearly the same crystal structure. The differences between these samples are that the relative intensity of the diffraction peak is decreased and its half-width is broader with increasing 1-octadecanol content. This is due to the interference between the 1-octadecanol and the soft–hard segments of the PUs. The addition of 1-octadecanol prevents the soft–hard segments of PUs from crystallizing [24]. The crystalline changing trend with increasing amounts of 1-octadecanol is generally consistent with that obtained from DSC analysis.

### *3.6. Mechanical Properties*

Mechanical properties of hydrogels are very important for pharmaceutical applications [2]. The tensile strength, Young's modulus, and tear strength were evaluated. A summary of the mechanical properties is given in Table 3. The mechanical test of the polymers showed that the tensile strength decreased slightly with the addition of 1-octadecanol while the tear strength increased in some content. The result suggests that small amounts of 1-octadecanol do not significantly affect the mechanical properties.

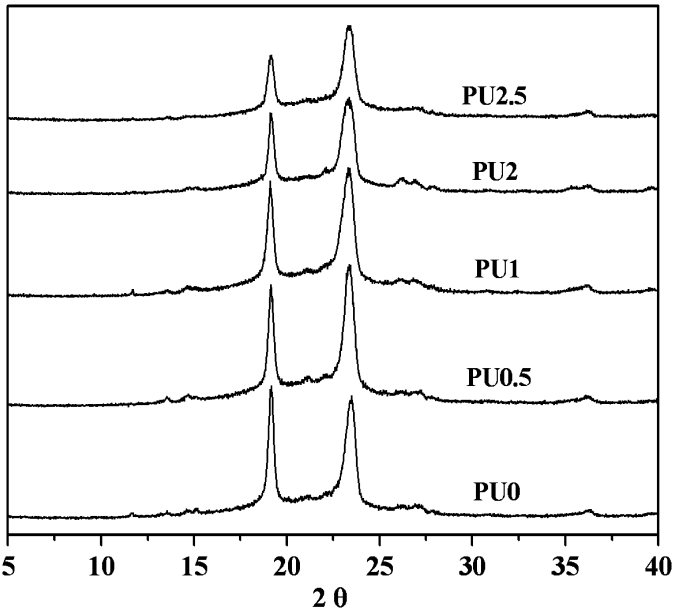



**Figure 4.** WAXD spectra of the basic polyurethane hydrogel and their 1-octadecanol additives.

**Table 3.**
Mechanical properties of polyurethanes

| Polyurethane | Tensile strength (MPa) | Young's modulus (MPa) | Tear strength (N/mm) |
|---|---|---|---|
| PU0 | 9.35 | 29.18 | 45.76 |
| PU0.5 | 8.31 | 56.92 | 58.79 |
| PU1 | 8.64 | 30.41 | 45.96 |
| PU2 | 8.71 | 35.49 | 49.31 |
| PU2.5 | 8.16 | 31.71 | 46.74 |

### *3.7. Swelling Ability*

For hydrogels, the equilibrium swelling ratio is strongly related to the chemical structure of the polymer [2], which is measured to understand the drug release behavior [8]. At the same time, the dynamic swelling experiment is conducted to characterize the water imbibition process [25]. Figure 5 shows the equilibrium swelling ratio and the swelling profile of hydrogels which was measured at 37°C. With the increase of 1-octadecanol addition, we found a consistent increase of the equilibrium swelling ratio. Generally, the water uptake of polymer blend is strongly influenced by its hetero-phase structure. When hydrophobic material grafting polyurethane components are swelling in water, the water diffuses through the hydrophilic phase. At a fixed composition, the water-uptake ratio decreases as the degree of intermixing increases [26]. In Fig. 5, PU2.5 shows the highest equilibrium

Downloaded by [University of Chicago Library] at 11:27 10 October 2014

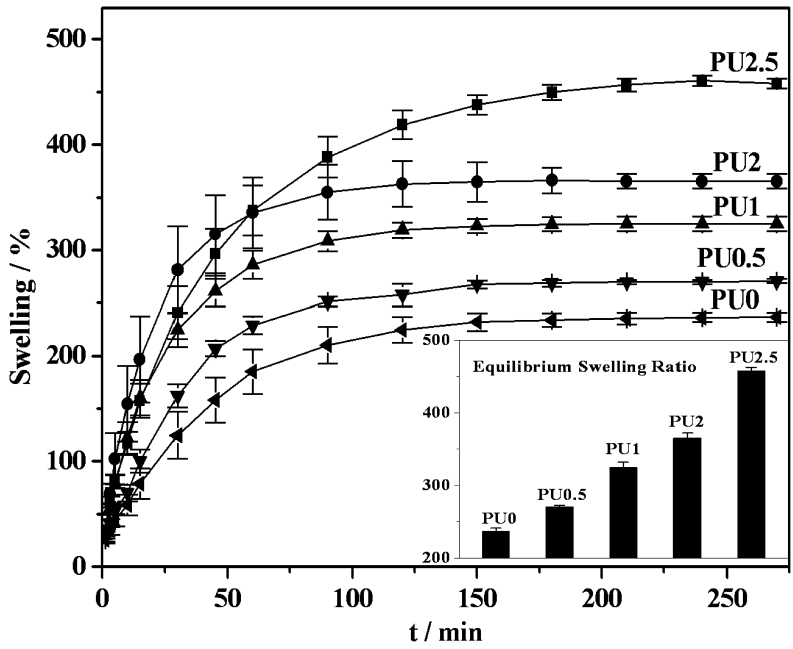



**Figure 5.** Swelling behavior of polyurethane hydrogels. Error bars represent the standard deviations for three experiments. Solid lines are the corresponding fits using equation (1); Column aspects are the corresponding fits using equation (2).

swelling ratio, which is attributed to its lowest degree of intermixing among the samples. Intermixing is consistent with the cross-link density. The cross-link density will decrease with increasing amount of 1-octadecanol added. 1-Octadecanol is mono-function hydrophobic material which can terminate the polymerization when reacting with MDI. The more 1-octadecanol is added, the lower the cross-link density is. Therefore, PU2.5 shows the highest equilibrium swelling ratio.

### *3.8.* In Vitro *Drug Release*

Tinidazole can be loaded successfully onto the polyurethane hydrogels. No drug particles precipitated or sedimented out of the loading solution before or after incubation. Loaded swollen hydrogels were clear and retained the original appearance of blank swollen hydrogels. Curves of rates of tinidazole release from the polymers are shown in Fig. 6. PU2.5 was the best one among the samples. The Ritger–Peppas equation (equation (3)) was used to analyze the drug release mechanically. In this equation, when the sample geometry is cylindrical and diffusion parameter $n = 0.45$–$0.89$, the diffusion mechanism is non-Fickian [27]. The sample PU2.5 ($n = 0.70$) presented a non-Fickian release mechanism with a regression coefficient ($R^2$) of 0.99, respectively. Therefore, the drug release is controlled by both swelling and diffusion control.

Downloaded by [University of Chicago Library] at 11:27 10 October 2014

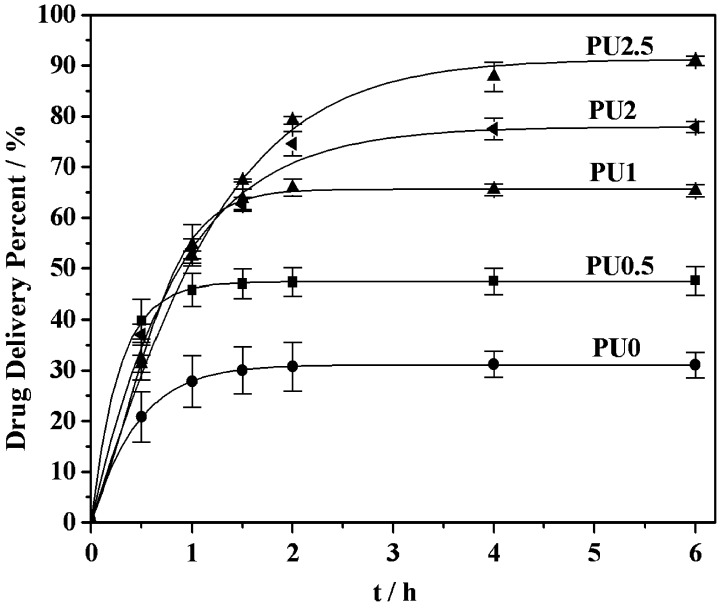



**Figure 6.** Cumulative release of tinidazole from the polyurethane hydrogels. Error bars represent standard deviations for three experiments.

Comparing cumulative drug-release profiles with swelling profiles suggested that the drug-release profiles were consistent with the swelling profiles and that the drug-release profile could be affected by changing the hydrogel's swelling profiles. Therefore, the addition of 1-octadecanol is an effective method to affect the drug-release profile.

In the PU hydrogel system, the model drug release times are affected not only by the polymers but also the model drug. In this study, tinidazole is used as model drug and it can sustain the drug release for 3 h. In terms of drug-release time, it is not a faultless model drug; further studies on other model drugs are being undertaken.

## 4. Conclusions

In this study, PUs were synthesized from PEG 6000, TMP and MDI as diol, diisocyanate and chain-extending agent, respectively. To regulate the drug-delivery profiles, a hydrophobic long-chain alcohol (1-octadecanol) was incorporated into the hydrogels by a simple method. The synthesized materials were characterized by FT-IR, DSC, WAXD and mechanical tests. The results showed that the use of 1-octadecanol would not change the structure, crystalline and mechanical properties obviously. It was also found that the swelling properties can be tailored to a wide range (235–460%) by changing the amount of 1-octadecanol. The *in vitro* drug-release results showed that the drug release profile of tinidazole was consistent with the swelling properties of hydrogels. The technique investigated here offers a

Downloaded by [University of Chicago Library] at 11:27 10 October 2014

relatively simple method to alter the drug-release profiles in hydrogel systems by changing their swelling properties and the polymer-based PU hydrogels could be used as potential matrices for vaginal drug delivery.

*Acknowledgements*

This study is financially supported by National Natural Science Foundation of China (30772662), Program for New Century Excellent Talents in University (NCET-06-0499), Ministry of Education key project (107062), grant from the Ph.D. Programs Foundation (20070316004) and 111 Project from the Ministry of Education of China and the State Administration of Foreign Expert Affairs of China (No. 111-2-07). D. Y. and C. J. contributed equally to this work.

Downloaded by [University of Chicago Library] at 11:27 10 October 2014

## References

1. A. Hussain and F. Ahsan, *J. Control. Rel.* **103**, 301 (2005).
2. N. A. Peppas, P. Bures, W. Leobandung and H. Ichikaw, *Eur. J. Pharm. Biopharm.* **50**, 27 (2000).
3. A. S. Hoffman, *Adv. Drug. Deliver. Rev.* **43**, 3 (2002).
4. K. Mequanint, A. Patel and D. Bezuidenhout, *Biomacromolecules* **7**, 883 (2006).
5. A. A. Calder and I. Z. Mackenzie, *J. Obstet. Gynaecol.* **17**, 53 (1997).
6. N. Morimoto, Y. Iwasakia, N. Nakabayashi and K. Ishihara, *Biomaterials* **23**, 4881 (2002).
7. X. Huang, B. L. Chestang and C. S. Brazel, *Int. J. Pharm.* **248**, 183 (2002).
8. L. F. Wu and C. S. Brazel, *Int. J. Pharm.* **349**, 1 (2008).
9. S. Jameela, N. Uma and A. Ayakrishnan, *J. Biomater. Sci. Polymer Edn* **8**, 457 (1997).
10. P. Kurt and K. J. Wynne, *Macromolecules* **40**, 9537 (2007).
11. N. Morimoto, A. Watanabe, Y. Iwasaki, K. Akiyoshi and K. Ishihara, *Biomaterials* **25**, 5353 (2004).
12. T. K. Mandal, *Eur. J. Pharm. Biopharm.* **50**, 337 (2000).
13. G. Lligadas, J. C. Ronda, M. Galià and V. Cádiz, *Biomacromolecules* **8**, 686 (2007).
14. S. A. Guelcher, A. Srinivasan, J. E. Dumas, J. E. Didier, S. McBride and J. O. Hollinger, *Biomaterials* **29**, 1762 (2008).
15. G. Lligadas, J. C. Ronda, M. Galià and V. Cádiz, *Biomacromolecules* **8**, 1858 (2007).
16. X. H. Kong and S. S. Narine, *Biomacromolecules* **8**, 2203 (2007).
17. F. Papadimitrakopoulos, E. Sawa and W. J. MacKnight, *Macromolecules* **25**, 4682 (1992).
18. D. J. Skrovanek, S. E. Howe, P. C. Painter and M. M. Coleman, *Macromolecules* **18**, 1676 (1985).
19. S. Mondal and J. L. Hu, *J. Membr. Sci.* **274**, 219 (2006).
20. M. X. Qiao, D. W. Chen, T. N. Hao, X. L. Zhao, H. Y. Hu and X. C. Ma, *Int. J. Pharm.* **345**, 116 (2007).
21. X. H. Kong and S. S. Narine, *Biomacromolecules* **9**, 1424 (2008).
22. J. L. Hu and S. Mondal, *Polym. Int.* **54**, 764 (2005).
23. J. C. Su and P. S. Liu, *Energ. Convers. Manage.* **47**, 3185 (2006).
24. X. J. Loh, K. B. C. Sng and J. Li, *Biomaterials* **29**, 3185 (2008).
25. N. A. Peppas and P. Colombo, *J. Control. Rel*. **45**, 35 (1997).
26. J. H. Kim and S. C. Kim, *Biomaterials* **23**, 2015 (2002).
27. O. Bayraktar, O. Malay, Y. Özgarip and A. Batıgün, *Eur. J. Pharm. Biopharm.* **60**, 373 (2005).