

Dependence of Biodegradation and Release Behavior on Physical Properties of Poly(caprolactone)-Based Polyurethanes

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ABSTRACT: Simultaneous pursuit of long accurate release control and high biodegradation rate is required as the membrane of controlled-release devices in agriculture. The effect of the physical properties of poly(caprolactone) based polyurethanes as a polymer membrane on their biodegradation characteristics and the release profile was evaluated. The soil burial test at 28°C resulted that the biodegradation rate of the polyurethanes increased as the number of average molecular weight (M_n) of poly(caprolactone) diol used increased from 500 to 1000, whereas it decreased as the M_n of poly(caprolactone) diol increased from 1200 to 2000. The biodegradation behavior was different when the M_n of poly(caprolactone) diols was used

because of the recrystallization of long straight poly(caprolactone) chains. Poly(caprolactone) triol prevented recrystallization and led the high degradation ratio. The release rate of urea from the polyurethane-coated granules decreased as the M_n of poly(caprolactone) polyol decreased. These results indicated that the release profile was affected by the urethane content, and the biodegradation characteristic was affected by the glass transition temperature and the recrystallization of polyurethane membrane. © 2009 Wiley Periodicals, Inc. *J Appl Polym Sci* 114: 246–253, 2009

Key words: biodegradable; drug delivery system; membranes; polyurethanes

INTRODUCTION

Controlled-release technology has been very important in many fields such as medicine, agrochemical industry, and household pest control.^{1–3} In agriculture, control of their release pattern and release rate of chemicals makes it possible to reduce the treatment times, which lead to labor saving, prevention of phytotoxicity, and excess release of agrochemicals into the environment. In fact, some controlled-release formulations, such as microcapsules, coated granules, granular matrixes and so on, have been developed. Furthermore, degradable polymers as coating materials are required to reduce the amount of residual polymer in the agricultural field. But it is very difficult to find a polymer with both long accurate release control and high biodegradation rate under the mild conditions of agricultural field.

Matrix-type devices using biodegradable polymers have been investigated eagerly in the pharmaceutical field. Poly(lactic acid) is one of the representative bio-

degradable polymers, and its release property can be changed by some methods such as changing the molecular weight of polymer, making copolymer with other polymers, blending with other polymer, or improving the manufacturing process, but the biodegradation is also changed at the same time.^{4–11} Therefore, it is very important to find the independent parameters of release of drugs and biodegradation of membrane. Wada et al. discussed the hydrolytic degradation and controlled-release of matrix device using a copolymer made of lactic acid and caprolactone. Its hydrolytic degradation was affected by the glass transition temperature (T_g) and the dynamic modulus. The release profile was affected by the molecular weight, T_g , the crystallinity, and the hydrolysis.⁴ The release pattern of matrix-type devices follows a first-order release,^{12,13} and the release rate was accelerated by the degradation of matrix polymer in some cases. On the other hand, there have been very few reports on coating and granular-type device using biodegradable polymer.¹⁴ This type of controlled-release system is very useful in the agriculture because it allows zero-order release or sigmoidal release pattern.^{14–22} Nonbiodegradable polymer capsules containing drug have been usually used in agriculture. After releasing the drugs, the nonbiodegradable polymer capsules

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TABLE I
Formulations of Polyurethane Membranes

| Sample name | Polyol | M_n of polyol | [NCO]/[OH] | Polymeric MDI cont. ^a |
|-------------|-----------|-----------------|------------|----------------------------------|
| PU-500D | PCL diol | 530 | 1.00 | 33.8 |
| PU-800D | | 832 | 1.00 | 24.5 |
| PU-1000D | | 984 | 1.00 | 21.5 |
| PU-1200D | | 1246 | 1.00 | 17.8 |
| PU-2000D | | 2004 | 1.00 | 11.9 |
| PU-500T | PCL triol | 552 | 1.00 | 42.3 |
| PU-800T | | 864 | 1.00 | 31.9 |
| PU-2000T | | 2004 | 1.00 | 16.8 |

^a [Polymeric MDI weight / total reactant weight] \times 100 (%).

are left in the field. Therefore, biodegradable polymer capsules are required.

Polyurethane is a very useful polymer because its physical and chemical properties can be easily modified within a wide range.²³ The biodegradation of polyurethane has also been reported.^{24–26}

In this study, the effects of T_g , storage modulus, tensile strength, and cross-linkage density of polyurethanes were investigated based on their release profiles and biodegradation characteristics. Biodegradation characteristics were evaluated by a soil burial test at 28°C reproducing conventional use. Controlled-release was evaluated by preparing polyurethane-coated granules.^{27–32} Urea, which is used as a fertilizer in agriculture, was selected as the water-soluble chemical in this study.^{15,16} Generally, sustained release of water-soluble drugs is more difficult in coating-type devices because their release rate is affected by the difference of the concentration, inside and outside the capsules. We also discuss herein the key physical and chemical properties of the membranes that affect their biodegradation characteristics and release profile.

EXPERIMENT

Materials

Poly(phenylene methylene isocyanate) (polymeric MDI) (Sumidur 44V-10; Functionality, $f = 2.3$ – 2.5) as an isocyanate was procured from Sumika Bayer Urethane, Japan. Poly(caprolactone) polyols (PCLs) as polymer glycols were procured from Daicel Chemical Industries, Japan. The M_n of the poly(caprolactone) diols (PCL diols) were 530, 832, 984, 1246, and 2004, and that of poly(caprolactone) triols (PCL triols) were 552, 864, and 2004. Granular urea was manufactured in China and its average diameter was about 3 mm, and the number of granules in 1 g was about 60–65.

Preparation of polyurethane films

The polyurethane films were prepared by the following method. The composition is shown in

Table I. The reactant ratio of isocyanate to hydroxyl was set at 1.00 : 1.00. Polymeric MDI was added to PCL melt at 70°C and vigorously stirred to be uniform for about 60 seconds. The viscous reactants were casted on a glass plate using an applicator; the thickness was set at 125 μm for the biodegradation test in soil due to shorten a test term and 375 μm for the physical and chemical tests. The glass plate was kept in the oven at 70°C for 3 h, and the termination of the reaction was confirmed by the disappearance of the isocyanate absorption at 2277 cm^{-1} by Fourier transform infrared spectroscopy (FT-IR) using ATR method (PerkinElmer Spectrometer; Spectrum One).

The sample name was designated as follows: PU, 500 and D and T mean polyurethane, M_n of PCL, and diol and triol, respectively.

Measurement of dynamic viscoelasticity

The temperature dependence of dynamic viscoelasticity was measured with a Rheovibron Auto Dynamic Visco Elastometer DDV-01FP (A&D Company, Japan). The measurements were performed from -150 to 250°C at a heating rate of 5°C min^{-1} under a nitrogen atmosphere. The imposed amplitude and frequency were set at 10 μm and 10 Hz, respectively.

Tensile test

Tensile test was performed using an Autograph (Shimadzu Autograph AGS-100A, Japan) at 25°C under 50% relative moisture. The size of the polyurethane films was 5.0 mm \times 100 mm \times 375 μm . The initial length and elongation rate were 30 mm and 30 mm min^{-1} , respectively.

Hydrolysis test

Polyurethane films with 125 μm thickness were immersed in buffer solutions of pH 2, 7, and 11 at 70°C. The films were removed after 7 days and washed in water. The dried weights of the films were measured, and the reduction rate of weight was calculated (pH 2 buffer solution: 50 mM disodium

hydrogenphosphate solution was added into 200 mL of 50 mM phosphoric acid solution to adjust pH 2. pH 7 buffer solution: 50 mM sodium dihydrogenphosphate solution was added into 200 mL of 50 mM disodium hydrogenphosphoric acid solution to adjust pH 7. pH 11 buffer solution: 50 mM phosphate acid solution was added into 200 mL of 50 mM trisodium phosphoric acid solution to adjust pH 11.)

Measurement of maximum water content

Polyurethane films were put into water at 25°C for more than 7 days until no further increase in the weight of the films was detected. Maximum water content was calculated from eq. (1).

$$\begin{aligned} \text{Maximum water content (\%)} \\ = \frac{[(\text{weight of wet film}) - (\text{weight of dried film})]}{(\text{weight of dried film}) \times 100} \quad (1) \end{aligned}$$

Biodegradation test in soil

Polyurethane films were cut into a size of 20 mm × 20 mm, and the initial weights were measured. Then, the films were buried in soil in a field in Hyogo Prefecture, Japan (clay loam soil having a moisture content of 25.9%, 40 g of soil was used for a film in a cup, 50 cups on a rack were covered by a polyethylene bag) and preserved at 28°C in the oven in the dark. During preservation, water was sprayed as required to keep the moisture of the soil constant. Each film was recovered after 1, 2, 3, and 6 months. The films were washed with water after microscopic examination, and they were dried to measure the weights. Then, the weight reduction rates of the films were determined.

Water vapor transmission rate (WVTR)

About 10 mL of water was put into the petri dish (6 cm in diameter). Polyurethane films with about 125 μm thickness were attached by silicone-based binding agent, which was commercially available. Then, the accurate weight was measured and put into the temperature- and humidity-controlled oven at 25°C and 0%. The weight was measured every 24 h for 7 days under the atmosphere. The constant rate of weight decreasing per hour [mg mm⁻²] was determined, and the value was normalized to that of the film with 100 μm thickness using eq. (2).³³

$$\begin{aligned} \text{Normalized WVTR (WVTR}_{100}) \text{ [mg mm}^{-2}\text{]} \\ = \text{Observed WVTR} \times \text{thickness of film}/100 \quad (2) \end{aligned}$$

Preparation of polyurethane-coated granular urea

The formulations of membranes are shown in Table I. Granular urea, 1000 g by weight, was made into tum-

bling and was heated up to 70°C using hot air. About 5.0 g of the viscous reactant, which was prepared by adding polymeric MDI to PCL melt at 70°C and vigorously stirred to be uniform for about 60 seconds, was added to the granular urea and the tumbling condition at 70°C was kept for 5 min. Further, the addition procedure of the viscous reactant was repeated until the total added amount reached 100g. The polyurethane-coated granules were after-cured for 15 min at 70°C. Termination of the reaction was confirmed by the disappearance of the isocyanate absorption at 2277 cm⁻¹ by FT-IR spectroscopy. Thereafter, the coated capsules were cooled down to an ambient temperature to obtain polyurethane-coated granular urea.

Release test

The granular urea capsules of 7.5 g were placed in 100 mL of water at 25°C. A measure of 0.50 mL of the solution was taken out at the required time. The urea content in the solution was determined by the colorimetry with UV-absorbance at 420 nm as follows. The coloring agent was a mixture of 20.0 g of *p*-dimethyl aminobenzaldehyde and 100 mL of hydrochloric acid in water of total 1000 mL. The coloring agent of 20.0 and 29.5 mL of water was mixed with 0.5 mL of sample solution. The color of mixed solution contained urea that changed to yellow by Ehrlich reaction. The content of urea was determined by UV-absorbance at 420 nm using calibration curve.^{34,35}

Maximum release rate as the apparent release rate constant was determined from the slope in the graph of release ratio (wt%) to the time (day).

RESULTS AND DISCUSSION

Physical properties of polyurethane films

Appearance of the obtained films was brownish transparent except for PU-1200D and PU-2000D, which was whitish opaque.

The mechanical properties, T_g , and maximum water content are summarized in Table II. Figure 1 shows the temperature dependence of the storage modulus (E') of polyurethane-based PCL diols [Fig. 1(a)] and PCL triols [Fig. 1(b)]. At an ambient temperature, only PU-500T, which has the highest urethane content, was glassy, and PU-800T and PU-2000D were leathery. The other polyurethane films were in an elastic state. The T_g is denoted as a temperature at which the storage modulus of glassy state sets in to decrease. With increase of M_n of PCL diol, T_g and storage modulus in the rubber plateau decrease, and the slope of glass transition region except that of PU-2000D was the same. This

TABLE II
Physical and Chemical Properties of Polyurethane Membranes

| Sample name | Appearance ^a | Urethane content ^b (%) | T_g (°C) | E^c | | Young's modulus ^d (MPa) | Max. water cont. (%) |
|-------------|-------------------------|-----------------------------------|------------|------------|-------------|------------------------------------|----------------------|
| | | | | 25°C (MPa) | 150°C (MPa) | | |
| PU-500D | BT, G | 11.9 | -6.0 | 7.3 | 7.4 | 3.5 | 1.29 |
| PU-800D | BT, R | 8.6 | -30.1 | 3.3 | 3.7 | 2.6 | 0.83 |
| PU-1000D | BT, R | 7.6 | -33.3 | 4.2 | 4.7 | 2.9 | 0.82 |
| PU-1200D | WO, R | 6.3 | -39.9 | 4.1 | 5.1 | 2.5 | 0.73 |
| PU-2000D | WO, L | 4.2 | -48.6 | 226.2 | 1.4 | 136.9 | 0.36 |
| PU-500T | BT, G | 14.9 | 47.0 | 1896.3 | 18.9 | 1600 | 1.45 |
| PU-800T | BT, L | 11.2 | 8.7 | 56.4 | 16.6 | 29.7 | 0.99 |
| PU-2000T | BT, P | 5.9 | -37.7 | 6.1 | 8.7 | 5.4 | 0.56 |

^a BT: brownish transparent, WO: whitish opaque, G: glassy, R: rubbery, L: leathery, P: plasticity.

^b Weight ratio of urethane bonds to total weight.

^c Storage modulus.

^d Young's modulus at 25°C.

tendency in PCL triol-based polyurethanes was the same as that of PCL diol-based polyurethanes. The results indicate that these polyurethanes have a micro phase-mixing phase. The storage modulus of PU-2000D showed a two-step dependence on temperature. The transition at lower temperature around -50°C was assigned to the glass transition. The PCL chain occurred because of the recrystallization at -50°C, which was due to begin the micro-Brownian motion. The storage modulus kept higher values due to the reinforced effect of crystallites. The transition at a higher temperature around 30°C was assigned to the melting of the crystallites.

The relationship between urethane content and T_g is shown in Table II. The T_g increased as the urethane content was increased. The PCL triol-based polyurethanes had a higher T_g than the PCL diol-based polyurethanes. The results indicated that the T_g of the polyurethane depends on the urethane content and the cross-linkage density.

Young's moduli determined from the stress-strain curves are shown in Table II. Young's modulus decreased as the urethane content decreased except

for PU-2000D. The tendency was the same as that of the storage modulus at 25°C.

The maximum water content in the polyurethane films increased as the urethane content increased, as shown in Table II. The maximum weight of water content of all polyurethanes was very small, and the polyurethane films were found to be hydrophobic.

It was concluded from the physical and chemical test that the polyurethane films were hydrophobic and had a wide range of physical properties, of which T_g changed from -49 to 47°C, and the Young's modulus from 2.5 MPa to 1600 MPa. These properties were determined from the urethane content and the cross-linkage density.

Biodegradation

After the soil burial test, the appearances of polyurethane films were brownish, and some filamentous fungus and bacteria were observed by scanning electric microscopy and the surface of the film was invaded. The result of the biodegradation test in soil for 6 months is shown in Table III. Degradation ratio

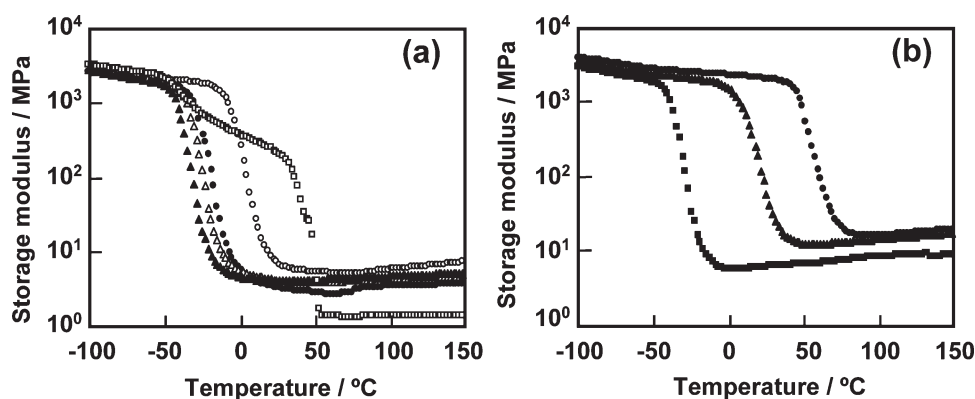


Figure 1 Temperature dependence of storage modulus of polyurethanes. (a) PCL diol-based polyurethanes, ○: PU-500D, ●: PU-800D, △: PU-1000D, ▲: PU-1200D, □: PU-2000D, (b) PCL triol-based polyurethanes, ●: PU-500T, ▲: PU-800T, ■: PU-2000T.

TABLE III
Degradation Characteristics and Release Properties of Polyurethane Membranes

| Sample name | Hydrolysis | | | Biodegradation Degradation ratio for 6 months (wt %) | Lag time (day) | Release properties | |
|-------------|--------------------|------|-------|--|-------------------|--|---|
| | Degradation (wt %) | | | | | Release rate const. (wt % day ⁻¹) | WVTR ₁₀₀ (mg mm ⁻²) |
| | pH 2 | pH 7 | pH 11 | | | | |
| PU-500D | 1.1 | 0.3 | 1.3 | 11.3 | nd | 5.5 | 0.0041 |
| PU-800D | 1.3 | 0.6 | 1.4 | 20.4 | nd | 19.5 | 0.0046 |
| PU-1000D | 1.2 | 0.5 | 1.6 | 31.6 | nd | 23.2 | – |
| PU-1200D | 0.9 | 0.4 | 1.1 | 30.6 | nd | 67.6 | – |
| PU-2000D | 1.0 | 0.2 | 1.6 | 9.7 | nd | 61.7 | – |
| PU-500T | 1.2 | 0.4 | 0.6 | 0.3 | 10 | 1.9 | 0.0035 |
| PU-800T | 0.9 | 0.4 | 0.4 | 1.3 | nd | 3.3 | 0.0042 |
| PU-2000T | 0.5 | 0.7 | 1.3 | 54.3 | nd | 59.5 | – |

nd: not detected; –: untested.

of PU-1200D after soil burial test was 67 wt % as a maximum and that of PU-500T was 1.9 wt % as a minimum value. However, the value of hydrolysis with very severe condition was from 0.2 to 1.6 wt%. The values by hydrolysis were very small weight loss compared with the loss after soil burial test. From the results, it was concluded that the weight reduction observed after soil burial test was mainly caused by the biodegradation.

Figure 2 shows the relationship between the weight reduction ratio (degradation ratio) of the polyurethane films after the soil burial test for 1 to 6 months and the urethane content. The degradation ratio of each polyurethane film increased with testing time. Figure 3 shows the relationship between T_g and the degradation ratio at 6 months. The degradation ratio increased as the T_g decreased except for PU-2000D. When T_g was more than 0°C, biodegradation rate was very low. In the case of the PCL diol-based polyurethane films, the degradation ratio of the films increased as the M_n of PCL diol increased in the range of 500 to 1000, in which the urethane content changed from 11.9 to 7.6 wt %. The maximum degradation ratio after 6 months was shown in PU-1000D.

However, the degradation ratio decreased as the M_n of PCL diol increased from 1200 to 2000, in which the urethane content changed from 6.3 to 4.2 wt %, although the T_g of polyurethanes was decreased. It was speculated that the decrease of biodegradation rate in PU-2000D was ascribed to the formed crystallites from the results of the storage modulus. In the PCL triol-based polyurethane, PU-500T and PU-800T had almost no degradation in which state of the films at tested temperature was glassy state and glass transition state, respectively, from the result of storage modulus. The degradation ratio of PU-2000T showed the highest at 54 and 56 wt %, respectively, after 3 and 6 months, which was higher than that of all of PCL diol-based polyurethane films.

Figure 4 shows the time dependence of the degradation ratio of PCL diol-based polyurethane films. The degradation rate of PU-1000D was the fastest during the first 3 months. The degradation rate of only PU-1200D and PU-2000D during the next 3 months was faster than that during the initial 3 months. The results indicate that the initial degradation rate of polyurethane film based on high molecular weight PCL diol was slow. The gradual

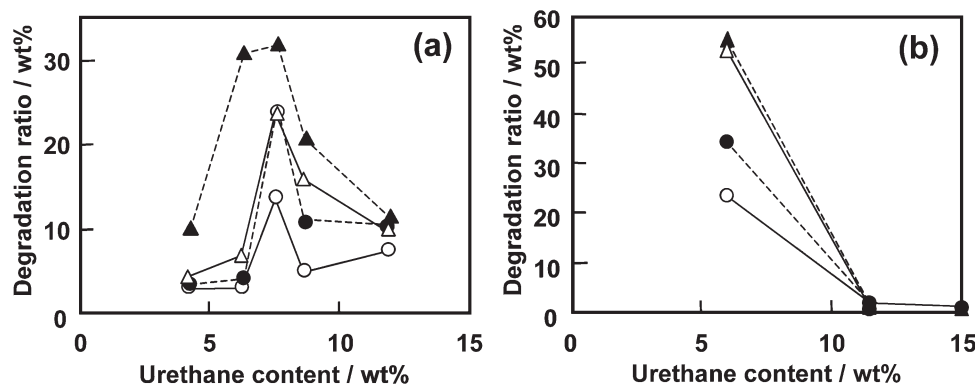


Figure 2 Weight reductions of the polyurethane films after the soil burial test for 1 to 6 months. (a) PCL diol-based polyurethanes, ○: 1 month, ●: 2 months, △: 3 months, ▲: 6 months. (b) PCL triol-based polyurethanes, ○: 1 month, ●: 2 months, △: 3 months, ▲: 6 months.

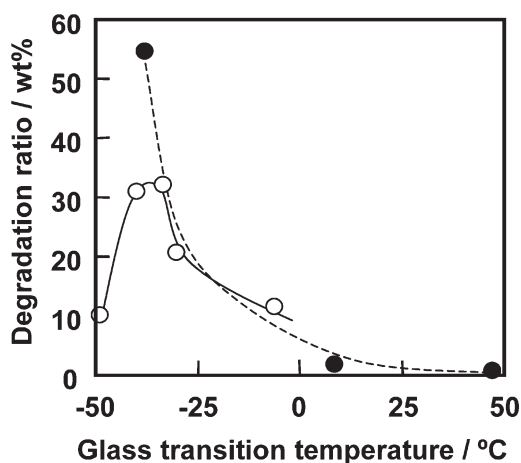


Figure 3 Relationship between the glass transition temperatures and the biodegradation ratio of the polyurethane films after the soil burial test for 6 months. ○: PCL diol-based polyurethanes, ●: PCL triol-based polyurethanes.

acceleration of degradation may affect the recrystallization of polyurethane films, and the degradation of PU-1200D would be affected by the crystallites effect of long PCL chains slightly because of its lower initial degradation rate than that of PU-1000D.

The degradation rate of PU-2000T during the first 3 months was faster than that during the next 3 months, although the urethane content was almost the same as that of PU-1200D. This difference would be due to the difference in their structures. The branched structure of PCL triol would prevent the occurrence of the crystallites of the PCL chain by the steric hindrance.

From the previous results, it was concluded that when the polyurethane films were based on PCL triol or low molecular weight PCL diol, that is, when the length of straight structure of PCL chains

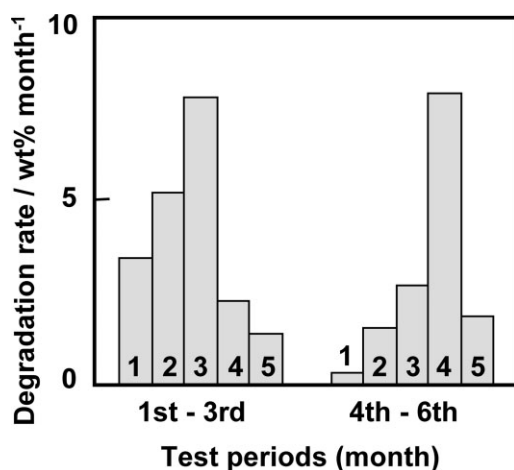


Figure 4 Degradation rates of the diol-based polyurethane films in a soil during the first 3 months and next 3 months. 1. PU-500D, 2. PU-800D, 3. PU-1000D, 4. PU-1200D, 5. PU-2000D.

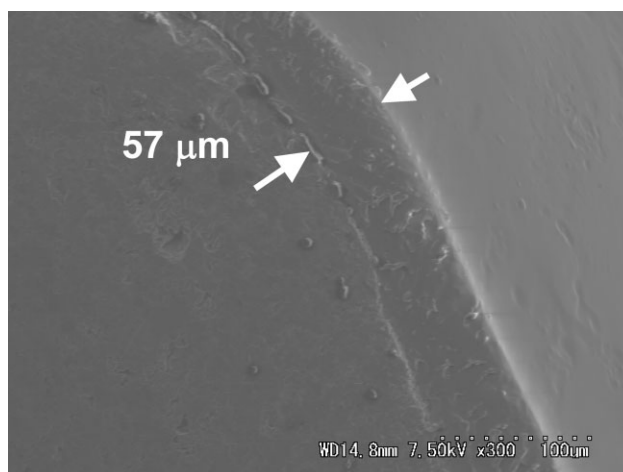


Figure 5 SEM picture of the cross section of polyurethane-coated granules (PU-1000D).

was short, the interaction among the PCL chains was weaker, and molecular mobility remained high. Consequently, the initial biodegradation rates were faster. The biodegradation rates of the polyurethane films with longer straight PCL chains were slow because of the crystallinity of the PCL chains, but the degradation rates gradually accelerated.

Release properties

Figure 5 shows the scanning electric micrograph of the cross section of the granular urea capsule prepared with PU-1000D. It was confirmed that the thickness of the membrane was about 50 μm , and it was a continuous membrane without defects.

Avi Shaviv et al.¹⁹ mentioned about the three-step release mechanism of drug from the polymer-coated capsule:

1. Water vapor penetration into the capsules during the lag period,

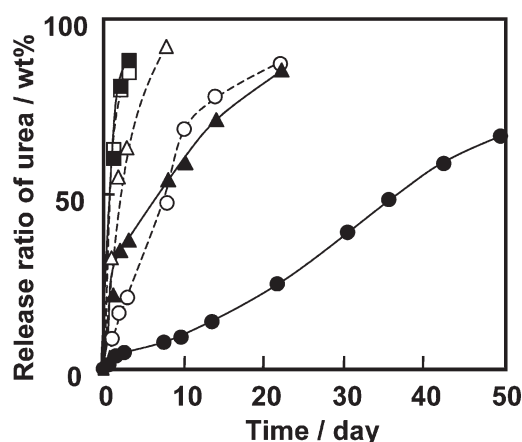


Figure 6 Release profiles of urea from the polyurethane-coated granules. ○: PU-500D, △: PU-1000D, □: PU-2000D, ●: PU-500T, ▲: PU-800T, ■: PU-2000T.

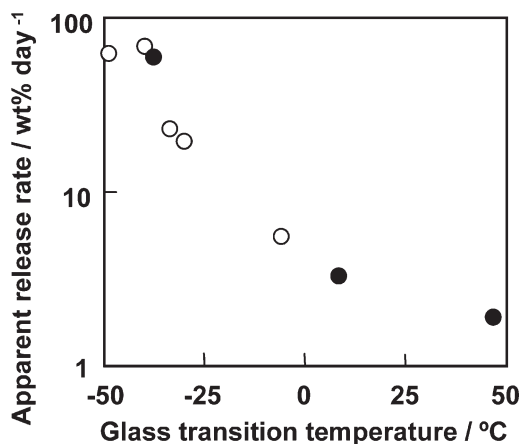


Figure 7 Relationship between the apparent release rate constants from polyurethane-coated granules and the glass transition temperatures. ○: PCL diol-based polyurethanes, ●: PCL triol-based polyurethanes.

2. Constant release as long as the solution inside is saturated,
3. Slowdown of release rate after the decay of saturation states of solution inside.

Some structural change of membrane, such as stretching of membrane, decrease of thickness, or rearrangement of microstructure, may happen before transitioning into the second step, because the expansion of capsule is occurred by continuous water vapor penetration caused by osmotic pressure by urea. The polyurethane-coated granules are also expected to obey this mechanism.

Figure 6 shows the release profiles of urea from the granular capsules coated with polyurethanes. The lag time and the apparent release rate constant obtained from the maximum slope of the release profiles are shown in Table III. PU-500T achieved the longest sustained release, and the lag time was observed after a small amount of burst release because of the defect of the membrane. On the other hand, the lag time was not observed in the other profiles. It would be caused by the fast water vapor permeation which increased as the urethane content decreased, as shown in Table III, and the lag time would be within 24 h.

Basically, chemical property of membrane related to water permeation or urea permeation will also be affected strongly on the apparent release rate. In addition, some mechanical property related to the structural change of membrane may be affected because of the release mechanism. The apparent release rate constant decreased as the urethane content increased, and that of PCL triol-based polyurethanes were smaller than that of PCL diol-based polyurethanes by comparison with the same urethane content (comparison of PU-500D and PU-

800T). Figure 7 showed the relationship between apparent release rate constant and the T_g . The effect of recrystallization observed on PU-2000D was not observed like biodegradation and the apparent release rate constant decreased to the ascent of the T_g , and the plots for the PCL diol-based polyurethanes and PCL triol-based polyurethanes were on the same curved line. From the result, it was found that the T_g or some parameter related to T_g can affect the release properties, supplementarily.

DISCUSSION

From the results of the biodegradation and the release test, T_g was one of the most effective parameters for both properties. And it was suggested that triol was also a significant parameter for both good biodegradation and slow release because it inhibited the recrystallization of PCL chains and led high structural resistance to the expansion of capsule by continuous water inversion.

CONCLUSION

The biodegradation characteristics of polyurethane membrane were affected strongly by the T_g of polyurethane. Furthermore, biodegradation rate was affected by the recrystallization of polyurethane films, which was led from the long straight chains of PCL. On the other hand, the release property was not affected because of the recrystallization of polyurethane films, and the relation with water vapor permeability and T_g was observed. From these results, it was shown that the biodegradation characteristics of polyurethane and release property can be controlled independently by using proper straight length of PCL and cross-linking.

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