

Microspheres of Biodegradable Block Copolymer for Long-Acting Controlled Delivery of Contraceptives

Dedicated to the Memory of the late Professor Ichiro Sakurada

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ABSTRACT: Microspheres containing Norgestrel (MCN) were prepared from block copolymer of ϵ -caprolactone and DL-lactide (PCL-*b*-PLA) through solvent-evaporation process. The MCN produced at 10°C using soluble or wettable solvent bears fine and close surface which endows it a higher ability to control drug release. The block copolymer showed a double release mechanism—diffusion release contributed by PCL segment and erosion-caused release by PLA segment. The effects of these two pathways can be balanced by tailoring the ratio of CL/LA in PCL-*b*-PLA to such an extent that the erosion-caused release could just compensate the declined amount resulted from diffusion release and a whole zero-order kinetics can be actually achieved. Such a balance has been accomplished when the ratio of 60/40 is used which proved to be a promising controlled delivery system.

KEY WORDS Contraceptive Microspheres / Biodegradable Block Copolymer / Long-Acting Controlled Delivery System / Zero-Order Release / Diblock Copolymer / Poly(ϵ -caprolactone)-*b*-poly(DL-lactide) /

Over the past decade, biodegradable polymers have been widely studied as various short-term implanted devices. One of the potential applications is medical uses is to build sustained drug delivery system on which many developments have been made. Jackaniz,¹ Yolles,² and Beck *et al.*³) studied the so called long-acting contraceptive devices using polylactides (PLA) as carrier. Polin⁴ used copolymers of aminoacid as carrier. Pitt *et al.*⁵ studied many aliphatic polyester and found that poly (ϵ -caprolactone) (PCL) possessed expected drug-permeability but with very slow biodegradation. A random copolymer of CL and LA was made to improve pliability but always with fast degradability. Both PCL and

its random copolymer with LA used to make capsules containing contraceptives. Although all these preparations showed a relatively long-term controlled release in animal tests, yet none of them has been used practically to date. Among other things, the decline of the release rate is one of the main problems. In order to search some other way to face the problem, a series of block copolymers of ϵ -caprolactone and DL-lactide (PCL-*b*-PLA) was synthesized in our laboratory and showed some peculiarities. Its important character for medical uses is the microphase separation morphology which endows it with a controllable variability in degradation rate and also the drug release rate. In this paper we report the prepa-

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ration of injectable microsphere based on the block copolymer PCL-*b*-PLA with proposed mechanism for its zero-order release rate.

EXPERIMENTAL

Materials

The block copolymers were synthesized according to our previous method.⁶ All the above block copolymer samples were adjusted to almost the same molecular weight but different segment ratio of CL/LA so that an effective comparison could be made only based on ratio factor.

The drug used in this work is Norgestrel, a woman's contraceptive being used in clinical as daily or monthly scriptions.

Microspheres containing Norgestrel (MCN) were prepared by the solvent-evaporation process introduced by N.R Beck *et al.*³ with some modifications.

Measurement of Drug-Load in MCN

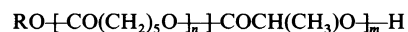
The microspheres are extracted with methanol for 5 h with a Fat Extractor. After the methanol is distilled out from the extractive phase, the extracted drug is dissolved in certain amount of absolute ethanol and measured UV spectrometrically.

In Vitro Drug Release Evaluation

Fast Comparison Test. In order to compare the release behavior of a series of samples within relatively short time, 20% aqueous solution of ethanol is used as release medium. Each sample is immersed into a given amount of ethanol solution which is maintained at 37°C under constant stirring. The amount of drug released is measured by UV spectrometer at regular intervals of time.

Long-Term Release Test. For long-term release, distilled water is used as release medium instead 20% ethanol. The release medium is collected daily and the drug released into the medium is extracted out with chloroform and

Table I. The general formula and physical parameters of PCL-*b*-PLA



Sample code	Monomer ratio	Copolymer properties		
	CL/LA mol	$[\eta]$	$\bar{M}_n \times 10^{-4}$	mp/°C
C-02	90/10	0.60	4.1	60
C-06	75/25	0.59	4.0	60
C-05	60/40	0.59	4.0	60

measured UV spectrometrically.

RESULTS AND DISCUSSION

Preparation on MCN

Process conditions and results for the preparation of MCN are listed in Table II. The obtained microspheres contain about 20% drug load with 90% in the recovery of MCN and 95% in drug-enclose efficiency. The shape of microsphere is mainly affected by the solvent used and the operation temperature. The microsphere prepared at 10°C has a compact spherical body with fine and close surface as shown in Figure 1. It bears rather narrow size distribution with major size range from 80 to 120 μm which is suitable for injection (see Figure 2). When the operation temperature is elevated to 20°C, some cracks and splits appeared on the surface of the sphere. If 35°C is used, no microsphere but irregular granule with big holes will be obtained (see Figure 3). From Table II, it is seen that when benzene which is neither soluble nor wettable for the drug is used, the drug-enclose efficiency would be greatly reduced. Although increasing the amount of acetone in acetone-chloroform mixture can speed up the sphere-forming, but it would lead to a terribly defective product like the one produced at 35°C. Figure 4 shows that the release rate of Norgestrel from the MCN prepared at 10°C is more slowly but steadily than the other temperatures. In order to prepare MCN with some perfect structure

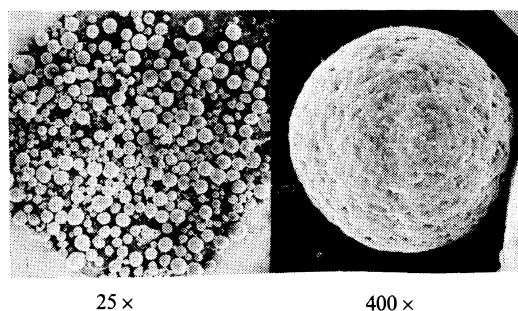


Figure 1. Scanning electron micrograph of MCN prepared at 10°C.

and the expected ability to control drug release, it is important to use a solvent which is both soluble and wettable for the drug and to evaporate the solvent slowly at lower temperature.

Release Mechanism of PCL-*b*-PLA Microsphere

Long-term release of Norgestrel from MCN of different block lengths in PCL-*b*-PLA was investigated *in vitro* and the results are given in Figure 5.

Table II. The process conditions and results for preparation of MCN

Test No.	Solvent v/v	Temp °C	Time h	Results				
				Drug load %	Shape	Size	Recovery of MCN %	Per cent of drug enclosed in MCN ^a %
						μm		
A-1	Benzene	10	27	10.2	Sphere	40—500	73.4	48.2
A-2	Acetone-chloroform (4:6)	10	24	19.5	Granule	—	91.8	92.9
A-15	Acetone-chloroform (3:7)	20	11	19.8	Sphere	40—400	86.2	94.3
A-5	Acetone-chloroform (3:7)	35	5	20.1	Granule	40—400	90.4	95.2
C-05	Acetone-chloroform (3:7)	10	30	19.7	Sphere	40—300	92.2	93.8
C-06	Acetone-chloroform (3:7)	10	30	19.8	Sphere	40—400	89.6	94.3
C-02	Acetone-chloroform (3:7)	10	30	19.7	Sphere	40—400	91.4	93.8

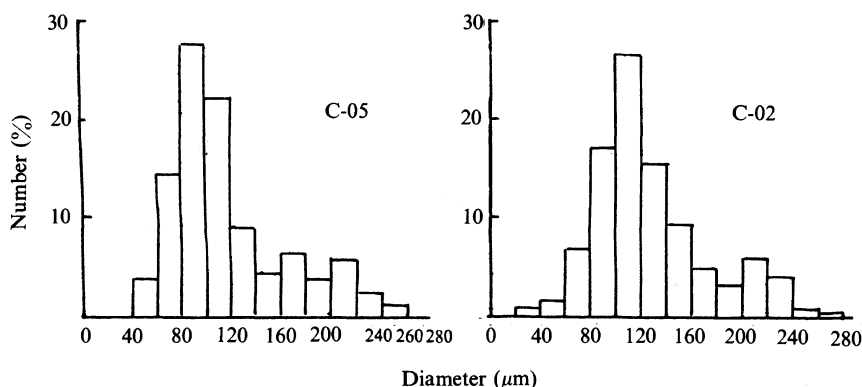


Figure 2. Size distribution of the MCN.

As mentioned above, the diblock copolymer of PCL-*b*-PLA would show an controllable variability in response to the ratio of CL/LA.

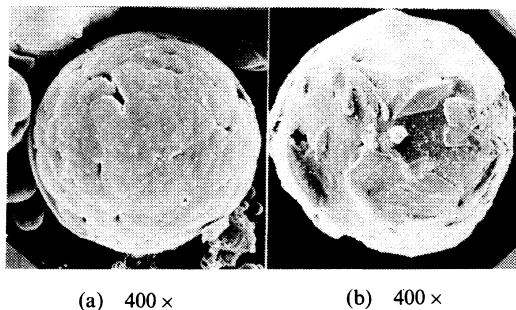


Figure 3. Scanning electron micrograph of MCN prepared at (a), 20°C and (b), 35°C.

PCL-*b*-PLA would show an controllable variability in response to the ratio of CL/LA. From Figure 5 we can see that although all the samples would maintain a sustained release for at least 6 months, they represent quite different rates and kinetics for microspheres of different composition. Line C-02 in Figure 5 shows the daily release of Norgestrel from MCN composed of 90% CL and 10% LA, which shows a declining rate with time like what has been seen with PCL homopolymer microsphere. Its percent release amount is linearly proportional to the square root of time which suggested a first-order kinetics (see Figure 6).

On the contrary, the MCN composed of

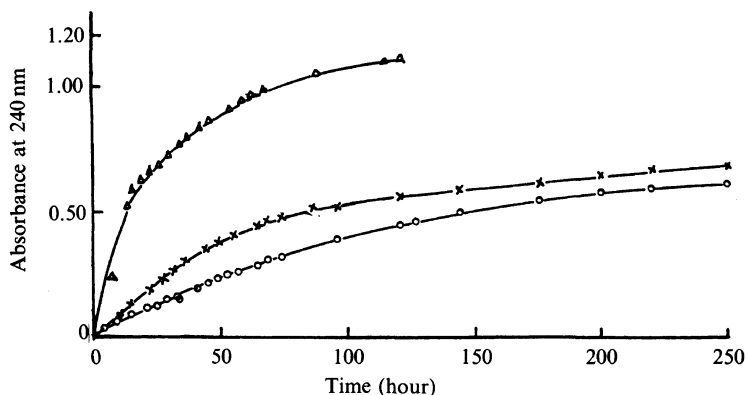


Figure 4. Comparison of release rate of Norgestrel from MCN prepared at different temperatures in 20% EtOH at 37°C. Δ - Δ , MCN of 35°C; \times - \times , MCN of 20°C; \circ - \circ , MCN of 10°C.

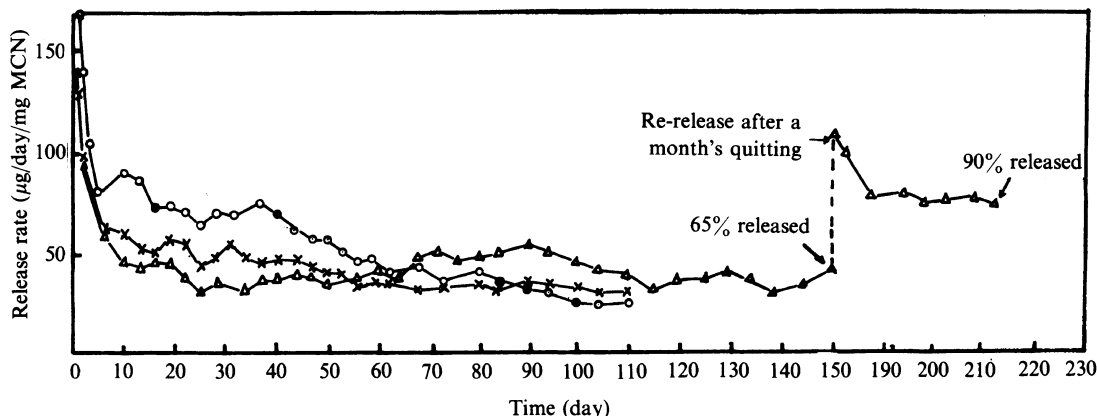


Figure 5. Daily release of Norgestrel from PCL-*b*-PLA microspheres with different segment ratio of CL/LA, *in vitro*, at 37°C. \circ - \circ , C-02; \times - \times , C-06; Δ - Δ , C-05.

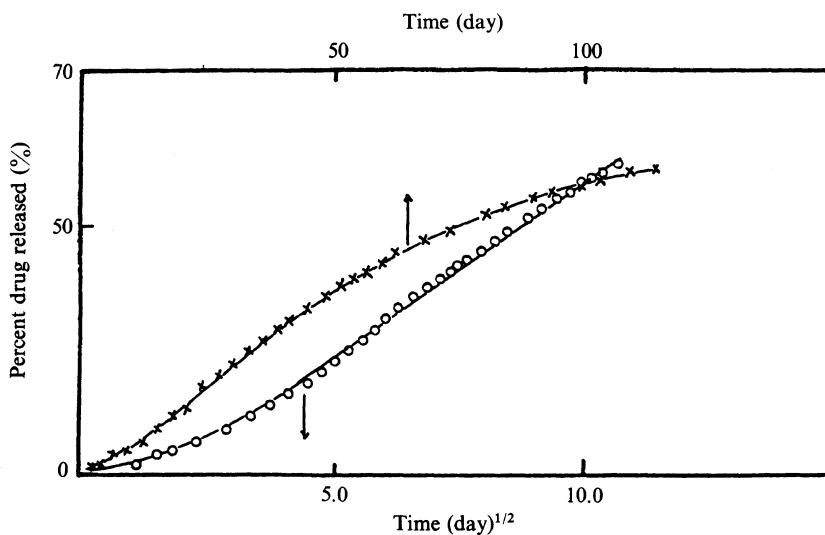


Figure 6. Cumulative release of Norgestrel from microspheres of PCL-b-PLA with 90/10 of CL/LA, *in vitro*, 37°C.

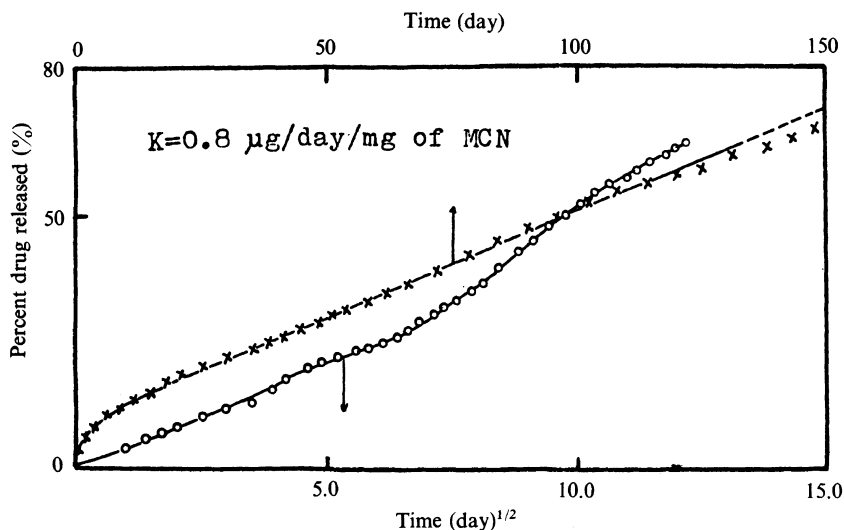


Figure 7. Cumulative release of Norgestrel from microspheres of PCL-b-PLA 60/40 of CL/LA, *in vitro*, 37°C.

60% PCL and 40% PLA (line C-05) shows almost a constant release for about 4 months without decline. Its percent release amount has almost a linear relationship with the one power of time, which showed a zero-order kinetics (see Figure 7). The rate constant was worked out to be $0.8 \mu\text{g/day/mg}$ of MCN at 37°C. It is supposed that using 100 mg of MCN could

provide a daily dosage of $80 \mu\text{g}$ for at least 4 months with single injection. The microspheres with 75/25 of CL/LA shows a middle release pattern between the other two extremes as shown in Figure 5 and Figure 8.

It is interesting to notice that the overall release kinetics has changed from first-order to zero-order when PLA segment ratio in the

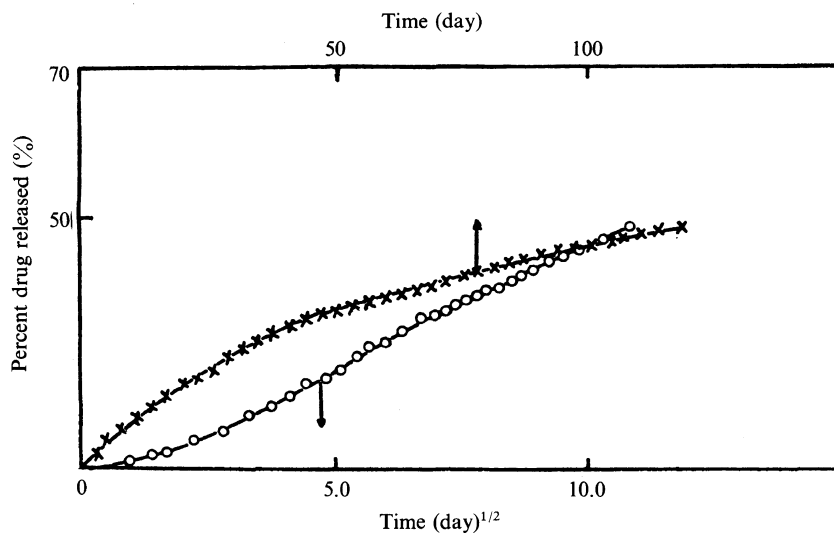


Figure 8. Cumulative release of Norgestrel from microspheres of PCL-*b*-PLA with 75/25 of CL/LA, *in vitro*.

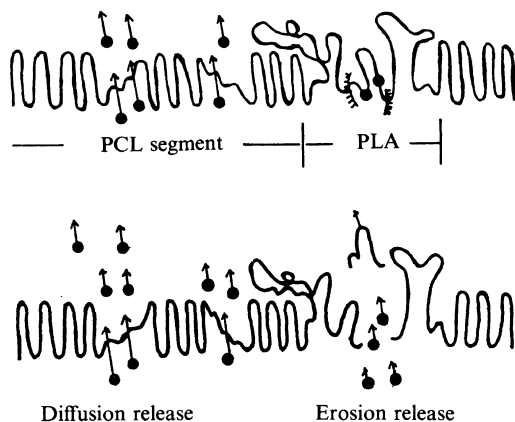


Figure 9. Schematic diagram of release mechanism for PCL-*b*-PLA.

block copolymer increases from 10% to 40%. This behavior may be attributed to the microphase separation morphology in PCL-*b*-PLA. As shown in Figure 9, the PCL segment in the block copolymer exists as semi-crystalline phase like PCL homopolymer which bears higher diffusion coefficient for most steroids but lower degradation rate. So the PCL segment mainly contributes the diffusion-controlled release which results in

the first-order kinetics just like that of PCL homopolymer. On the other hand, the PLA segment in the block copolymer would maintain its amorphous state like PLA homopolymer which degrades much more rapidly than PCL segment. As a result, the degradation rate of PCL-*b*-PLA inevitably dependent on the ratio of CL/LA, *i.e.*, increases with increasing PLA ratio. The degradation of PLA segment would result in an additional release, erosion-caused release, and would enhance drug release by leaving holes after some degradation. These effects would act as a good compensation for the rate decline resulted from PCL controlled diffusion release. By varying the ratio of PCL/PLA in the block copolymer, these two release pathways, diffusion and erosion, can be balanced to such an extent that the erosion-caused release could just compensate the declined amount in diffusion release and an overall zero-order release is actually achieved.

CONCLUSION

1. The block copolymer of ϵ -caprolactone and DL-lactide (PCL-*b*-PLA) is versatile in

controlling its biological functions such as biodegradation rate and drug release rate. By altering the ratio of CL/LA it is possible to predestine these properties to meet the precise needs for biodegradable and controlled drug delivery device.

2. The microsphere made of PCL-*b*-PLA showed a double release mechanism with a controllable manner. The effects of two pathways can be balanced by tailoring the CL/LA ratio to such an extent that a whole zero-order release can be achieved.

3. For Norgestrel-containing microsphere some better balance can be accomplished when the ratio of 60/40 is used. It presents a constant release period of around 4 months or more which proved to be a promising controlled delivery system for contraceptives.

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