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Drug release characteristics of multi-reservoir type microspheres with poly(DL-lactide-co-glycolide) and poly(DL-lactide)

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Abstract

For the multi-reservoir type microspheres composed of poly(DL-lactide-co-glycolide) (PLGA) and poly(DL-lactide) (PLA), the influence of the drug-holding layer and the non-drug-holding layer on drug release profiles was studied. The microspheres with the blend of PLGA and PLA were prepared by the W/O type emulsion-solvent evaporation technique, and cisplatin was used as a model drug. The degree of water uptake and the erosion of each polymer were evaluated to clarify the mechanism of drug release for multi-reservoir type microspheres. The blending of PLA and PLGA provided two types of microspheres in terms of the drug distribution in a microsphere, depending on the ratio of the blend: the microspheres with the drug-holding layer covered by the non-drug layer and the microspheres with the drug on the outer region. The drug release in the early period was governed by the pattern of drug distribution. The drug release rate at a steady state was governed by the erosion of the drug-holding layer. The results of present study indicate that drug release from multi-reservoir type microspheres involves the following process: (a) rapid release of the drug near the surface of microspheres, (b) formation of micropores in the non-drug-holding layer by hydration and erosion, (c) degradation of the drug-holding layer, and (d) diffusion of the drug through micropores.

Keywords: Microspheres; PLA; PLGA; Multi-reservoir type; Controlled release

1. Introduction

Interest in biodegradable poly(DL-lactide) (PLA)/poly(DL-lactide-co-glycolide) (PLGA) microspheres has been increasing because they are useful for injectable formulations providing long-term drug release. Some types of microspheres [1–4] have already been introduced to the medical field. However, the microspheres have some problems, such as 'initial burst,' which is the phenomenon that a large part of the encapsulated drug is released in a short time just after administration. Initial burst is suspected of causing side effects.

Recently, we developed a new technology of microencapsulation to reduce initial burst [5–7], which provided the multi-reservoir type microspheres with a unique structure: small droplets disperse in a microsphere, and the drug is localized in internal droplets.

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The preparation of multi-reservoir type microspheres is performed by the O/W type emulsion-solvent evaporation technique, using a blend of two or more polymers for the oil phase. The mechanism of the formation for multi-reservoir type microspheres is based on the following physicochemical phenomena that occur in the oil phase. One is the Dobry effect [8]: the blending of PLGA and PLA causes phase separation above a certain concentration even in a good solvent for both polymers. The other is the partition phenomenon of particles in biphasal solution: the particles localize in one phase according to the balance between the solubility parameters of the particles and each phase.

However, the mechanism of the drug release from this type of microsphere has not been clarified. The balance between the drug-holding layer and the non-drug-holding polymer layer may influence the drug release from the multi-reservoir type microspheres.

The purpose of this study is to examine the contribution of each layer to the drug release. The degree of the erosion and the water uptake of each polymer will be evaluated. 20 KDa PLA and PLGA were used, and cisplatin was used as the model drug. All experiments were validated beforehand to understand the phenomena as clearly as possible.

2. Materials and methods

2.1. Materials

Poly(DL-lactide) (PLA, molecular weight 20,000) and poly(DL-lactide-co-glycolide) (PLGA, molecular weight 20,000; lactide moiety/glycolide moiety ratio, 50/50) were purchased from Wako Pure Chemical Industries Ltd., Japan.

Cis-dichlorodiamineplatinum (||) (cisplatin) was obtained from Aldrich Chemical Company Inc., Germany. Poly(vinyl alcohol) was obtained from Nihon Synthetic Chemical Industries Ltd., Japan. All other materials and solvents were of reagent grade.

2.2. Methods

2.2.1. Preparation of microspheres

Cisplatin microspheres were prepared by the solvent preparation method, which was previously described [5]. Briefly, the blend of PLA and PLGA (900 mg) was dissolved in methylene chloride (1500 mg). The pulverized cisplatin crystals (approximate mean diameter: 1 μm) (100 mg) were dispersed in this solution. The resultant was emulsified into 0.5 wt.% poly(vinyl alcohol) solution (400 ml) with a Polytron® homogenizer (Polytron, Kinematica Ag Littau, Switzerland), at 12,000 rpm for 5 min at 15 °C to form oil-in-water emulsion. The temperature of the emulsion was gradually raised up to 30 °C to remove the solvent. The hardened microspheres were washed with water and filtered. The obtained microspheres were lyophilized. The mean size of the microspheres was 30 μm.

2.2.2. Microscopic observation

The distribution of cisplatin in a microsphere was observed using an optical microscope (DIAPHOT, Nihon Kogaku Ltd., Japan). The morphological change of the microspheres during an in vitro release study (see 'Section 2.2.4. In vitro release study') was observed by the following procedure. The cross-sections of the periodically collected microspheres were obtained by slicing microspheres. A piece of the cross-section was observed using a scanning electron microscope (S-2250N, Hitachi Ltd., Japan).

2.2.3. Determination of cisplatin content of microspheres

The microspheres were dissolved in methylene chloride (2 ml) and extracted into 0.001N HCl − 0.15M KCl solution (5 ml). The cisplatin in the aqueous phase was assayed by the HPLC method. Briefly, 4.6 mm × 250 mm Inertil ODS-2 (GL Science, Japan) was used. The mobile phase was 10 mM phosphate buffer containing 6 mM tetrabutylammonium (pH 2.8). The peak was detected at 301 nm.

2.2.4. In vitro release study

Microspheres (10 mg) were suspended in 10 ml of 9.6 mM phosphate-buffered saline (PBS; pH7.4) in test tubes, and then stirred at 25 rpm in an air chamber thermostated at 37 ± 1 °C. 9 ml of the supernatant was taken out and replaced by 9 ml of the fresh PBS at the predetermined day interval. The cisplatin in the collected supernatant was measured by the HPLC method described in "Determination of cisplatin content of microspheres."

2.2.5. Water uptake

Microspheres (15–20 mg) were suspended in 15 ml of PBS, and the mixture was stirred at 25 rpm, 37 °C. The microspheres were collected periodically and the surface water was removed by filtration and the wet weight (Ww) of the microspheres was recorded. The samples were dried under vacuum to a constant weight and the dry weight (Wd) was recorded. The water uptake was calculated according to the difference between Ww and Wd.

2.2.6. Polymer remaining during in vitro release study

Microspheres were incubated in the same condition as in the in vitro release study. The microspheres were collected periodically. The remaining polymer was assayed by the reported method [9]. The microspheres were dissolved in methylene chloride (2 ml), and 0.05N KOH–methanol solution (3 ml) was added to the solution. The resultant was incubated at room temperature for 3 h to hydrolyze the polymer into the monomers (lactide and glycolide). The solvent was removed under nitrogen at 50 °C. The monomers were assayed as lactic acid and glycolic acid by the HPLC method. Briefly, 4.6 mm × 250 mm Inertil ODS-2 (GL Science, Tokyo, Japan) was used. The mobile phase was 10 mM phosphate buffer containing 6 mM tetrabutylammonium (pH 2.8). The peak was detected at 210 nm.

The remaining ratios of the lactide moiety and the glycolide moiety were calculated by the following equation;

$$\text{The remaining the lactide moiety in the placebo of PLA microspheres (\%)} = \frac{(\text{Lactide acid from the remaining microspheres})}{(\text{Lactide acid from the initial microspheres})} \times 100$$

$$\text{The remaining the glycolide moiety in multi} - \text{reservoir type microspheres (\%)} = \frac{(\text{Glycolic acid from the remaining microspheres})}{(\text{Glycolic acid from the initial microspheres})} \times 100$$

2.2.7. Change of molecular weight during release study

The microspheres were incubated in the same condition as in the in vitro release study. The microspheres were collected periodically. The molecular weight of the collected microspheres was measured by the GPC system. Briefly, 7.8 mm × 300 mm

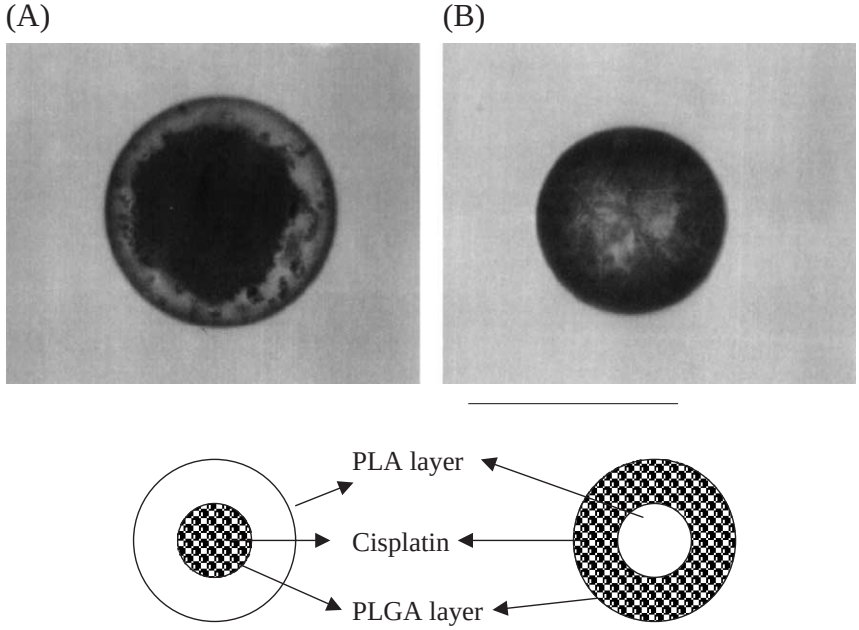


Fig. 1. Optical microphotograph of the typical multi-reservoir type microspheres. (A) Type A; localization of drug powder in internal layer, (B) type B; localization of the drug powder in external layer. The length of a bar indicates 50 μm.

TSKgel (G4000HXL, G3000HXL, G2000HXL) (Tosho, Japan) was used. The mobile phase was chloroform. A refractive index detector was used.

3. Results

3.1. Characteristics of microspheres

The microspheres were prepared by using the biphasic solution as the oil phase with various ratios of PLGA/PLA, containing cisplatin particles. As a typical example, the distribution of cisplatin particles in the microspheres is shown in Fig. 1. A lesser amount of PLGA than PLA provided the microspheres with the drug-holding layer covered by the non-drug layer (type A, Fig. 1A). On the other hand, a greater amount of PLGA than PLA provided the microspheres with the drug on the outer region (type B, Fig. 1B).

Table 1 shows the list of composition of polymers, the encapsulation efficiencies of cisplatin, and the type of the drug distribution in a microsphere. EX. 1 and EX. 2 had the morphology of the type A. On the other hand, EX. 3, EX. 4 and EX. 5 had the morphology of the type B. The encapsulation efficiencies were higher by 10–20% for type A than for type B.

3.2. Release of cisplatin from microspheres

To examine the influence of the morphological difference on the drug release from microspheres, in vitro release studies were performed on the five formulations listed in Table 1. Fig. 2 shows the cumulative release profiles. EX. 1 and EX. 2, which belonged to type A, showed similar release profiles in spite of the different composition of PLGA/PLA. EX. 3, EX. 4, and EX. 5, which belonged to type B, provided similar release profiles.

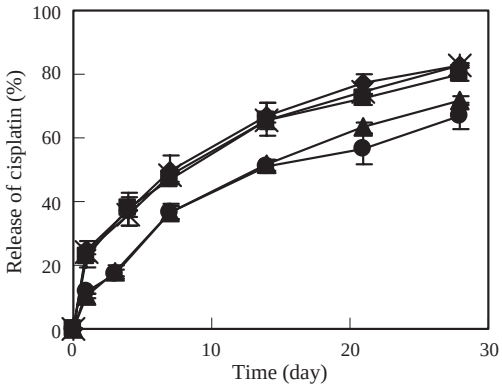


Fig. 2. Effect of the PLGA/PLA ratio on the drug release in 9.6 mM phosphate-buffered saline (pH7.4) at 37 °C. Batch numbers were EX. 1 (●), EX. 2 (▲), EX. 3 (■), EX. 4 (×), and EX. 5 (◆). 3 lots were prepared for each formulation. Data represent mean ± S.E.

The initial bursts were different between type A (EX. 1 and EX. 2) and the B type (EX. 3, EX. 4 and EX. 5). Type A showed approximately 10% release, however, type B showed about 25% release (Table 2).

To evaluate the drug release rate at a steady state, the mean release rate from each formulation from 7 to 28 days was calculated (Table 3). The release rates at a

Table 1
Percentage of each ingredient, encapsulation efficiencies, and type of microspheres

Batch number	Polymers	Ratio of polymers (%)	Loading of cisplatin (%)	Encapsulation efficiencies (%)	Type of microspheres
EX. 1	LGA5020[a]	18	10	105.8 ± 6.6	A
	LA0020[b]	72			
EX. 2	LGA5020	30	10	103.8 ± 2.2	A
	LA0020	60			
EX. 3	LGA5020	45	10	85.2 ± 2.2	B
	LA0020	45			
EX. 4	LGA5020	60	10	88.4 ± 1.0	B
	LA0020	30			
EX. 5	LGA5020	72	10	91.4 ± 3.4	B
	LA0020	18			

Data of encapsulation efficiencies represent mean ± S.E. of 3 lots.
[a] Poly(DL-lactide-co-glycolide) lactide/glycolide = 50/50, MW 20,000.
[b] Poly(DL-lactide) MW 20,000.

Table 2
Percentage of cisplatin release at day 1

Batch number	Release of cisplatin at day 1 (%)
EX. 1	12.0 ± 0.9
EX. 2	10.0 ± 1.1
EX. 3	23.0 ± 3.4
EX. 4	24.3 ± 1.4
EX. 5	24.6 ± 2.9

Data represent mean ± S.E. of 3 lots.

steady state were independent of the type of drug distribution in a microsphere and similar to the drug release from PLGA microspheres (data not shown).

3.3. Determinants of drug release

To clarify the determinants of the drug release from type A microspheres (multi-reservoir type microspheres), the erosion, the water uptake, the molecular weight change, and the morphological changes were studied. The degree of the erosion of each layer was studied. Fig. 3 shows the degree of the erosion and the cisplatin release of EX. 1 microspheres. The glycolide moiety of PLGA had decreased about 10% at day 1, followed by the gradual reduction of the glycolide moiety. About a half of the glycolide moiety was eroded by day 28. The residual PLGA corresponded to the residual cisplatin. On the other hand, the limited PLA had been eroded for 28 days, except for the period of 1–3 days.

To determine the change of PLA, the water uptake and the change of molecular weight were indirectly evaluated by using the placebo of PLA microspheres. The water uptake in the microspheres started in full after a 1-week lag, and reached approximately 8-fold of the dried microsphere weight (Fig. 4).

The change of molecular weight of the placebo of PLA microspheres is shown in Fig. 5. The molecular weight decreased linearly.

Table 3
Release rate at steady state

Mean of release rates (%/day) (7–28 day)	
EX. 1	1.36
EX. 2	1.68
EX. 3	1.51
EX. 4	1.61
EX. 5	1.54

Data represent mean of 3 lots.

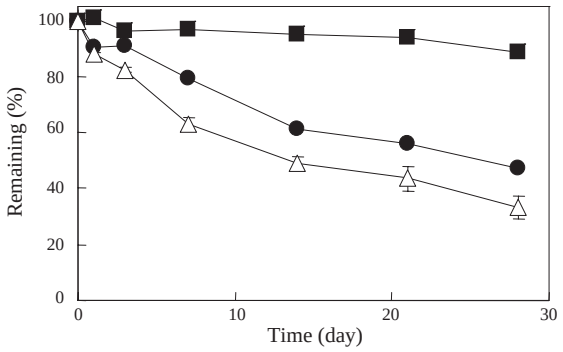


Fig. 3. Remaining the lactide moiety, the glycolide moiety and cisplatin in the microspheres during the in vitro release study; lactide moiety in the placebo of PLA microspheres (■), glycolide moiety in the multi-reservoir type microspheres (EX. 1) (●) and cisplatin in the multi-reservoir type microspheres (EX. 1) (△). Data represent mean ± S.E. of 3 lots.

The morphological change of EX. 1 microspheres during the release study was observed. No change was observed at day 1 (Fig. 6A). Micropores over the microsphere were observed at day 4 (Fig. 6B), and a large cavity at the center of a microsphere was observed at day 28 (Fig. 6C).

4. Discussion

In the previous paper [5], we reported that cisplatin particles were localized in the PLGA phase of the biphasic solution of the PLA–PLGA-solvent system.

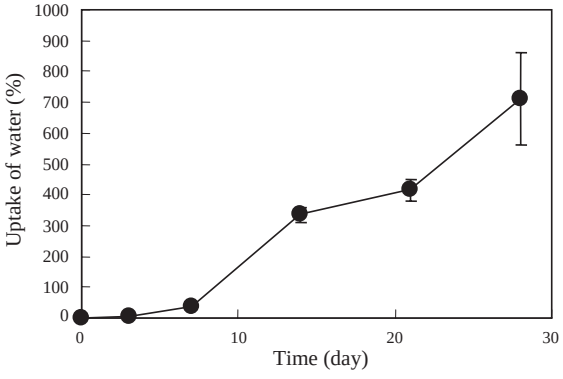


Fig. 4. Water uptake into the placebo of PLA microspheres in 9.6 mM phosphate-buffered saline (pH7.4) at 37 °C. Test solution was pH7.4. Data represent mean ± S.E. of 3 lots.

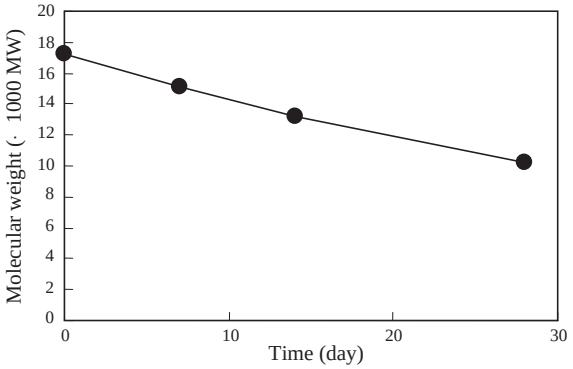


Fig. 5. Change of MW of the placebo of PLA microspheres in 9.6 mM phosphate-buffered saline (pH7.4) at 37 °C.

Although both PLA and PLGA were soluble in methylene chloride, the methylene chloride solution of their blend showed phase separation above a certain concentration. By the identification of each phase of PLA–PLGA-solvent biphasal solution by FT-IR, we concluded that the phase separation resulted from the incompatibility between PLA and PLGA. Moreover, the determination of the dispersion phase or the continuous phase for each polymer was controlled by the PLA/PLGA ratio.

In present study, it was clarified that two types of microspheres (type A and type B) on which the distribution pattern of the drug in the biphasic solution was reflected was obtained when cisplatin microspheres were prepared by using the oil phase with various PLA/PLGA ratios. This indicates that the distribution pattern of a drug in the biphasic solution is stable against the mechanical stress and the contact with water during the sequence emulsification process. For the stability of the dispersion system in the oil phase at the preparation of microspheres, the viscosity is one of the important factors. In the solid-in-

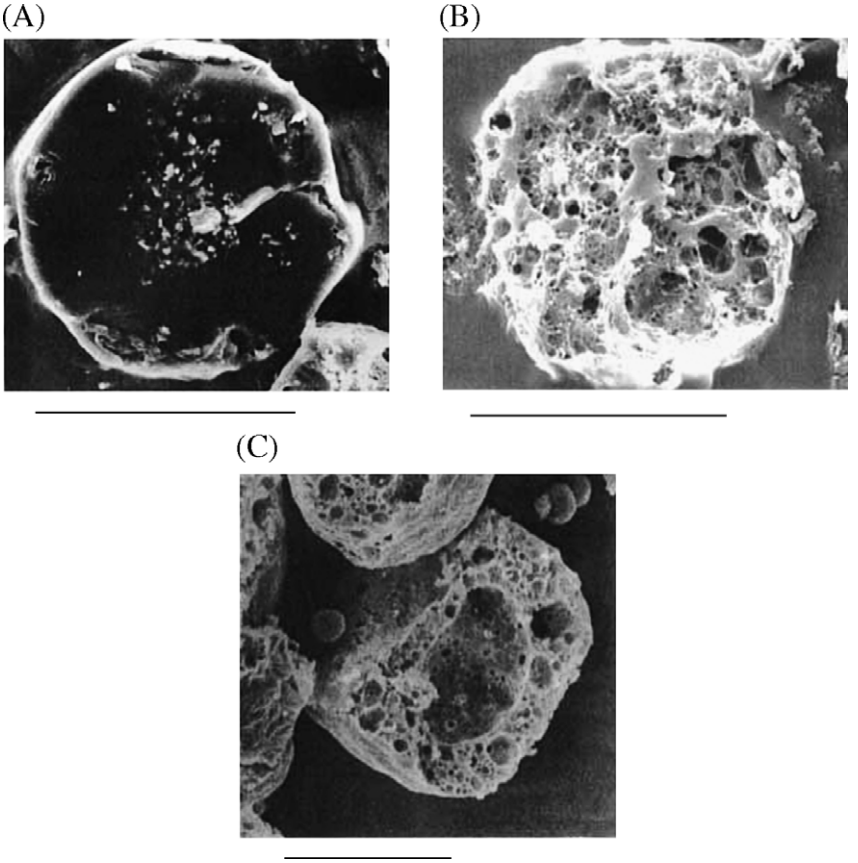


Fig. 6. Morphological change of the multi-reservoir type microspheres (EX. 1) during in vitro release study; scanning electron micrograph of cross-sections of microspheres at (A) day 1, (B) day 4 and (C) day 28. The length of bars indicates 50 μm.

oil system, it is reported that a relative high viscosity is needed to suppress the leakage of drug particles [10]. For the water-in-oil system, which is followed by preparing the water-in-oil-in-water system, it is reported that the high viscosity of both the water phase and the oil phase stabilized the system [11]. In the case of the PLGA–PLA-solvent system, a critical concentration for the formation of the biphasic system provides the relatively high viscosity of the system. The high viscosity of the PLGA phase and the PLA phase is considered to maintain the distribution pattern of the drug in the oil phase during the subsequent emulsification into the water phase. The encapsulation efficiencies were higher by 10–20% for type A than for type B. This indicates that for type A microspheres, the leakage of the drug into the water phase during the emulsification process and the solvent evaporation process could be suppressed effectively by preventing the distribution of a drug in the surface of a microsphere. In addition, we suppose that the condensation of a drug in a small area in a microsphere suppresses the dissolution of the poorly soluble drug, like cisplatin, into the water phase by reducing the dissolution during the preparation of microsphere. High encapsulation efficiency of type A (the multi-reservoir type) microspheres is an advantage for the industrial process.

By the drug release test of 5 formulations, it became clarified that the drug release patterns from the microspheres were influenced by the distribution pattern of the drug in a microsphere, rather than by the change of the blending ratio of polymers. At the part of the initial release, type A microspheres showed an approximately 10% release; on the other hand, B type showed about a 25% release. This is the evidence that the non-drug-holding layer (PLA layer) can improve the burst effect.

However, the approximate release rates at a steady state (7–28 days) of 5 formulations were 1.8%/day, independent of the distribution pattern of the drug in a microsphere. In addition, the release rate was similar to that of a steady state from PLGA microspheres. This indicates that the cisplatin release rate of a steady state is subject to the drug-holding layer, PLGA.

To evaluate the contribution of the PLGA layer and the PLA layer on the drug release, the degree of erosion, the degree of water uptake, the change of molecular weight, and the change of the morphological change were studied. In these studies, type A microspheres (EX. 1) were used to simplify the systems. The erosion by degradation is known to be one of the important determinants for the drug release from biodegradable microspheres [12,13]. Fig. 3 shows the degree of the erosion and the cisplatin release of EX. 1 microspheres. The erosion of the PLGA layer was evaluated as the residual glycolide moiety in the microspheres. The erosion of the PLA layer could not be measured directly; the lactide moiety is contained not only in PLA but also in PLGA, and the lactide moiety/glycolide moiety ratio of PLGA might be changed during the release study. Therefore, the erosion of the PLA layer was estimated from the residual lactide moiety in the placebo of PLA microspheres.

The glycolide moiety of PLGA had decreased by about 10% for 1 day. About a half of the glycolide moiety was eroded within 28 days. The residual glycolide moiety of PLGA corresponded to the residual cisplatin. This indicates that the erosion of the PLGA layer controls the disassociation of drug from the PLGA layer. On the other hand, the limited PLA had been eroded for 28 days, except for the period of 1–3 days. The erosion of PLA occurs after water-soluble oligomers are generated by the degradation. The limited erosion was anticipated to occur after day 3 because the degradation of PLA is slow. The erosion of PLA before day 3 is anticipated to be due to the degradation and the release of lower molecular weight oligomers, which originates from the raw material. The erosion of PLA at the early period is considered to lead to the production of micropores in the PLA layer of multi-reservoir type microspheres. The cisplatin disassociated from the PLGA layer can be released through these micropores.

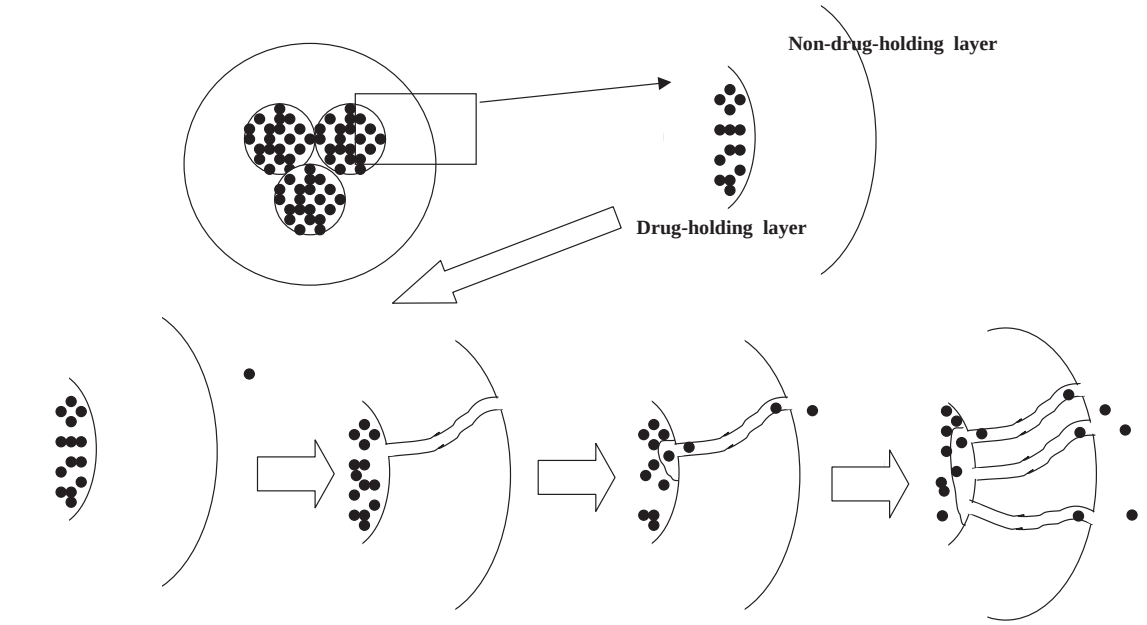
On the formation of micropores in the PLA layer, water uptake is also considered to play an important role. The formation of micropores in the PLA layer was indirectly evaluated by water uptake in the PLA placebo microspheres. The water uptake in the microspheres started after a 1-week lag and reached approximately 8-fold of the dried microsphere's weight. This indicates that the pores in the PLA layer increase in spite of the limited erosion in the PLA layer.

Batycky et al. suggest that the hydration through the micropores formed during the preparation process

is followed by the expansion of the pore walls by erosion [14]. The pore wall erodes slowly by its contact with water, and the pores increase to effective size for the diffusion of drug. According to Batycky's suggestion, the increase of micropores observed in our study is anticipated mainly to be in size, and not in number. However, little erosion was observed in our study in spite of the increase of the micropores. Lemaire et al. suppose that polymer erosion with loss of material is unlikely to take place in micropores, although a local weakening of the matrix occurs by polymer degradation [15]. Brunner et al. report that the osmotic pressure in the microspheres increases at the early period of drug release test [16]. Judging from these suggestions, we believe that micropores increase in size by weakening the matrix and increasing high osmotic pressure, rather than erosion.

To confirm the erosion of the PLGA layer and the formation of micropores by erosion and swelling in PLA layer, the morphological change of EX. 1 microspheres during the release study was observed. These findings confirm visually that a large amount of the erosion of the PLGA layer and the formation of micropores in the PLA layer occurred.

The mechanism of the cisplatin release from the multi-reservoir type microspheres, which is presumed by these results, is illustrated in Fig. 7. The drug release from the type A microspheres is considered to involve a more complicated process than the conventional monolithic microspheres. The process can be divided into the following four steps: (Step 1) rapid release of drug near the surface, (Step 2) formation of micropores in the PLA layer (non-drug-holding layer) by erosion and water uptake, (Step 3) erosion of the PLGA layer by hydrolysis, and (Step 4) diffusion of the drug through the increased micropores in the PLA layer. In case of the monolithic microspheres, (Step 1), (Step 3), and (Step 4) get involved in the drug release



	Step1	Step2	Step3	Step4
Non-drug-holding layer	Release of drug near the surface	Erosion of Low MW PLA		More effective pores in drug-free layer generated by repulsion among charged polymers
Drug-holding layer			Erosion of PLGA and drug release	Erosion of PLGA and drug release

Fig. 7. Hypothesis of the drug release mechanism from the multi-reservoir type microspheres (type A).

mainly. It is considered that (Step 1) involves the burst effect, and that (Step 3) and (Step 4) involve drug release at a steady state. Multi-reservoir type microspheres have one large advantage of a small contribution of the (Step 1), and another advantage is that we can choose various release profiles, based on the (Step 2). For instance, the facultative starting time of the drug release can be set by the control of the degree of the erosion or the swelling in the non-drug-holding layer and this will lead to wide application in the clinical field.

5. Conclusion

This study revealed the following: (i) the non-drug-holding layer (PLA layer) of the multi-reservoir type microspheres suppressed "initial burst" and the loss of the drug during manufacturing; (ii) the drug-holding layer (PLGA layer) controlled the rate of the drug release at a steady state, which is independent of the ratio of the non-drug-holding layer/drug-holding layer; and (iii) drug release from the multi-reservoir type microspheres was involved in the four processes. Among these processes, the erosion and the water uptake of the non-drug-holding layer and the erosion of the drug-holding layer are important processes to determine the profiles of drug release.

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