A New Drug Delivery System Using Plasma-Irradiated Pharmaceutical Aids. V. Controlled Release of Theophylline from Plasma-Irradiated Double-Compressed Tablet Composed of a Wall Material Containing Polybenzylmethacrylate

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A controlled-release tablet was obtained by oxygen plasma irradiation on the outer layer of double-compressed tablets prepared from theophylline as a core material and a copolymer of methylmethacrylate (MMA) and benzylmethacrylate (BzMA) as a single wall material, making this possible that polybenzylmethacrylate (PBzMA) has dual intramolecular functions, a plasma degradable main chain and a plasma-cross-linkable benzyl group in the side chain as an effect of plasma irradiation. It was shown that the dissolution profiles can be varied so as to cause release of theophylline at different rates, depending on the set of conditions chosen for tablet manufacture and for plasma operation.

Key words plasma-processing; double-compressed tablet; theophylline; polybenzylmethacrylate; controlled-release; DDS; ESR

We recently reported preparation of multilayered particles applicable for a drug delivery system (DDS) using plasma processing (Fig. 1).[1-6] Novel controlled-release tablets can be obtained by oxygen plasma irradiation generated by radio frequency discharges operating at 13.56 MHz on the outermost layer of double-compressed tablets. These tablets use theophylline as a core material and a mixture of plasma degradable polyoxymethylene (POM) and plasma-crosslinkable polystyrene (PST)[1,3,6] or bioerodible polylactic acid (PLA) in place of PST as a wall material.[2-4,6] The work has further been extended to preparation of the controlled-release tablet using bioerodible polycarbonate derived from bisphenol A (PC) as a single wall material; the polycarbonate is thought to have dual intramolecular functions: crosslinkable phenyl group and degradable carbonate group in the polymer main chain, as a plasma irradiation effect.[5,6]

In this paper, we used polybenzylmethacrylate (PBzMA) which has a plasma-degradable main chain and plasma-cross-linkable functional group in the side chain, and a copolymer of PBzMA and polymethylmethacrylate (PMMA), a plasma degradable polymer, for the outer layer of a double compressed tablet containing theophylline. We studied the effect of the polymer main chain and benzyl side chain in the theophylline release behavior from the plasma-irradiated double-compressed tablet, our purpose being to apply a new type outer layer polymer to this DDS preparation.

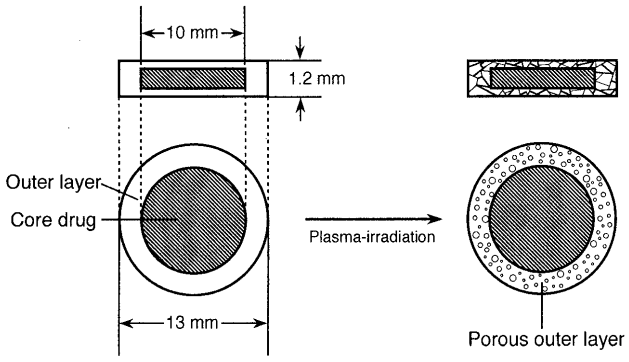


Fig. 1. Schematic Diagram of Plasma-Irradiated Double Compressed Tablet for Sustained-Release System

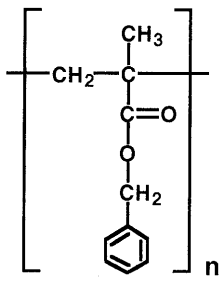
Experimental

Materials Commercial monomers, BzMA and MMA (Tokyo Kasei Kogyo Co., Ltd.) were purified before use by distillation. Commercial theophylline was dried *in vacuo* at 60 °C for 24 h and used without further purification.

PBzMA Preparation PBzMA was prepared by warming BzMA with 0.05% 2,2′-azo-bisisobutyronitrile (AIBN) as a radical initiator in benzene at 60°C in a sealed glass-made tube under nitrogen for 5 h, and was purified by precipitating in an excess amount of methanol. These polymers were then dried *in vacuo* at 60 °C for 24 h and screened through a 200-mesh sieve. The molecular weight of PBzMA powder thus obtained was number-average molecular weight ($\bar{M}n$) = 409000 and weight-average molecular weight ($\bar{M}w$) = 785000 ($\bar{M}w/\bar{M}n$ = 2.04) based on calibration of standard polystyrene. Both were determined by a gel permeation chromatograph (GPC) (Shimadzu LC-6A) equipped with a gel column (GPCKF-800p, GPCKF-80 m) at 40 °C, and a refractive index (RI) detector (Shimadzu, RID-6A) in THF as an elution solvent.

PMMA Purification PMMA was purchased from Nacalai Tesque, Inc. and was purifed by dissolving in $CHCl_3$ and precipitating in a large amount of methanol ($\bar{M}n$ = 230000, $\bar{M}w$ = 430000, $\bar{M}w/\bar{M}n$ = 1.84).

Copolymer Preparation For copolymer of MMA : BzMA = 5.2 : 1, a benzene solution (2 ml) containing BzMA (0.4 g, 2.3 mmol), MMA (1.6 g, 16.0 mmol) and AIBN (2 mg, 0.012 mmol) was warmed at 60 °C in a sealed glass-made tube under nitrogen for 30 min. The content was poured into a large amount of methanol, and the precipitated polymer was collected to yield 0.15 g (7.5%) of copolymer. Composition of the



Polybenzylmethacrylate (PBzMA)

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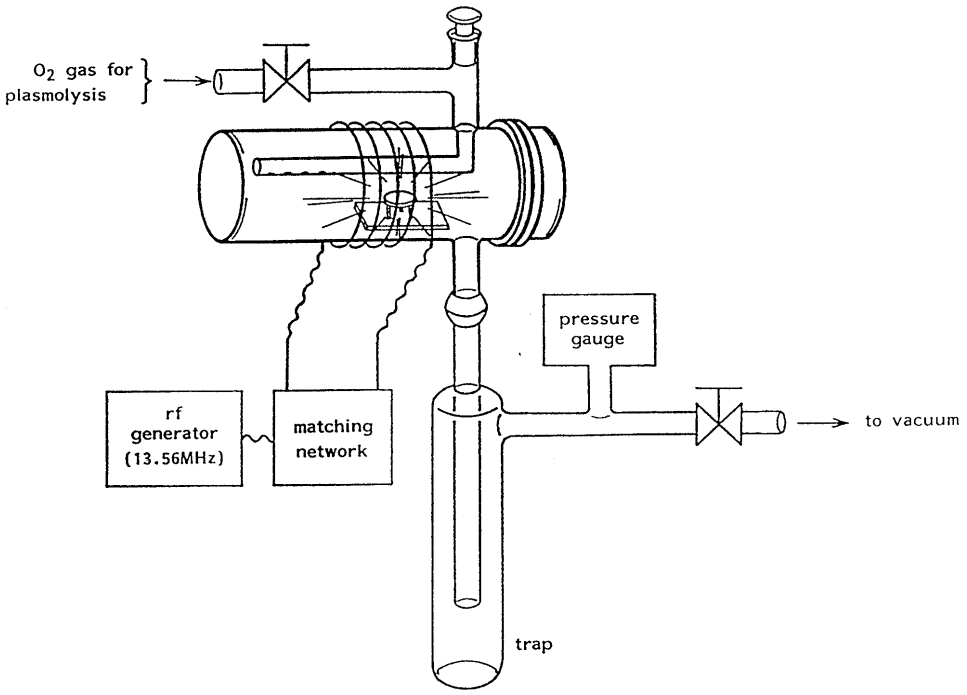

Fig. 2. Schematic Representation of Preparation of Plasma-Irradiated Sample

copolymer was determined by its ^{1}H-NMR spectra, and the copolymer thus obtained was purified by dissolving it in benzene and precipitating it in excess methanol. Then, these polymers were dried *in vacuo* at 60 °C for 24 h and screened through a 200-mesh sieve ($\bar{M}n = 330000$, $\bar{M}w = 550000$, $\bar{M}w/\bar{M}n = 1.66$). Copolymer of MMA : BzMA = 11.1 : 1 was obtained by warming BzMA (0.2 g, 1.2 mmol), MMA (1.8 g, 18.0 mmol) and AIBN (2 mg) in benzene (2 ml) in a manner similar to that described above. The yield was 0.19 g (9.5%) ($\bar{M}n = 340000$, $\bar{M}w = 550000$, $\bar{M}w/\bar{M}n = 1.62$). Copolymer of MMA : BzMA = 27.2 : 1 was obtained by warming BzMA (0.1 g, 0.6 mmol), MMA (1.9 g, 19.0 mmol) and AIBN (2 mg) in benzene (2 ml) as above; the yield was 0.20 g (10.0%) ($\bar{M}n = 360000$, $\bar{M}w = 580000$, $\bar{M}w/\bar{M}n = 1.62$).

Tablet Preparation Polymer tablets were obtained by compressing PBzMA powder and its copolymer powder (100 mg of the fractions screened through a 200-mesh sieve) into a flat-faced tablet, 13 mm in diameter, at a pressure of 200 kg/cm^2 for 30 s. Double-compressed tablets were also prepared at a pressure of 200 kg/cm^2 for 30 s from a flat-faced core theophylline tablet (10 mm in diameter, at a pressure of 40 kg/cm^2 for 10 s) and powdered polymer as a wall material. All flat-faced tablets were prepared using a hand press instrument (SSP-10A, Shimadzu Co.) in a tablet die (P/N 202-32010, Shimadzu Co.).

Plasma Irradiation A schematic representation of the apparatus for plasma irradiation is shown in Fig. 2, and is essentially the same as reported earlier.[1-6] The plasma state was generated by radio frequency (rf) discharges of inductive coupling using a four-loop antenna at 13.56 MHz with the supplied power of 30—50 W. Flow volume (50 ml/min) and pressure of oxygen gas or argon gas (0.5 Torr) for plasmolysis were controlled by changing the evacuation speed. The sample tablets were placed on a glasstripod in a reaction chamber to ensure homogeneous exposure to plasma gas. Degradation rate of polymer tablets induced by plasma irradiation was determined by measurement of the weight loss at various stages of plasma duration.

Electron Spin Resonance (ESR) Spectral Measurement Powdered PBzMA and its copolymer samples, 100 mg of the fraction screened through a 200-mesh sieve, were placed in a specially designed ampule (30 mm i.d., 100 mm long) connected with a capillary tube (2 mm i.d.) at the uppermost part of the ampule. The ampule was filled with argon gas for plasmolysis (0.5 Torr) and sealed. Then, the argon plasma state was sustained with supplied power of 40 W for the prescribed period of time while samples were stirred at room temperature. Then, the ESR measurements were performed while turning the ampule upside down after plasma irradiation, which is fundamentally the same procedure as that reported earlier.[7-20]

Dissolution Test Dissolution test of theophylline from the double-compressed tablets was conducted in distilled water, according to the standard dissolution method using a rotational basket apparatus (TR-5S3, Toyama Industry) at 37±0.5 °C with 100 rpm. Released theophylline was periodically assayed by UV absorption spectrum at the wavelength of 270 nm.

Scanning Electron Microscope (SEM) The surface characteristics of the plasma-irradiated tablet were examined by SEM (JEOL, JSM T-330A) (accelerating voltage:15 kV, magnification: × 500).

Results and Discussion

Degradation Property of PBzMA by Plasma Irradiation and Radicals Produced The degradation property of polymers by plasma irradiation is known to be dependent on the plasma reaction apparatus and shape of the samples. The release rate of theophylline from the double-compressed tablets is believed to be closely related to the degradation property of the outer layer polymers. We therefore studied the plasma degradation property of PBzMA focusing on the changes in the weight loss of the polymer directly-compressed tablets by plasma irradiation using the apparatus shown in Fig. 2.

Figure 3 illustrates changes in the weight loss of PBzMA directly-compressed tablets according to the oxygen and argon plasma irradiation time in comparison with the results obtained with PC and polyethyleneterephthalate (PET).

As is clear in this figure, PBzMA decreases in weight linearly with plasma irradiation time within the time studied, as true of two other bifunctional polymers, PC and PET. However, the degradation property of PBzMA with a crosslinkable part in the side chain is small compared with PC and PET which have a crosslinkable part in the main chain on oxygen plasma irradiation; the difference in the degradation property of PBzMA between oxygen plasma irradiation and argon plasma irradiation is also small compared with that of PC and PET, suggesting that the cross-linking reaction occurs more easily.

Figure 4 shows changes in the ESR spectra of radicals

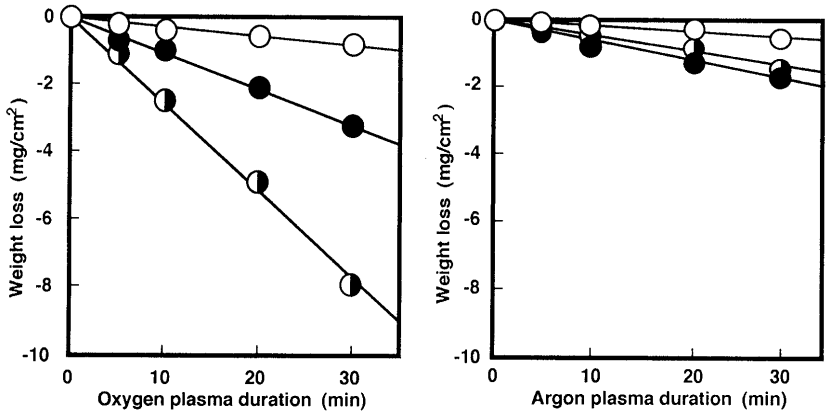

Fig. 3. Effect of Plasma-Irradiation on Polymer Degradation
Plasma conditions: 50 W, 0.5 Torr, O_2 or Ar 50 ml/min. ○, PBzMA; ●, PC; ◑, PET.

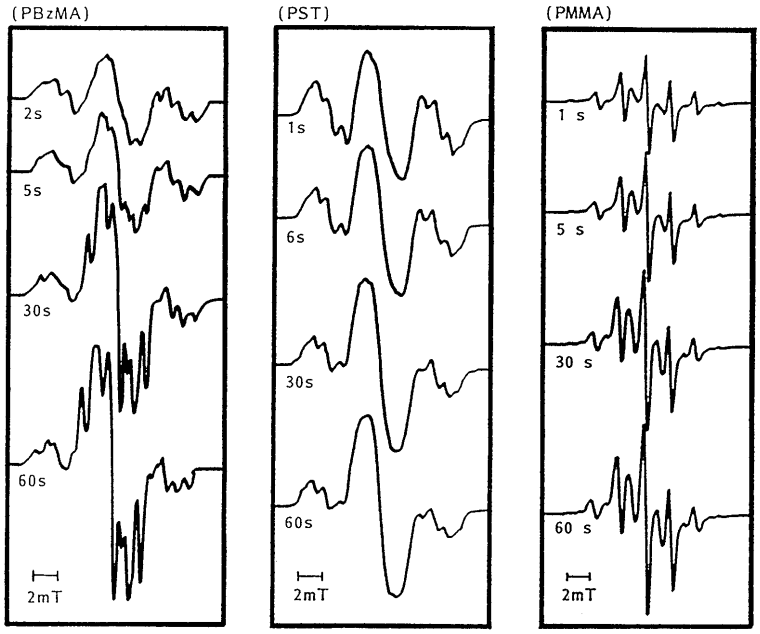

Fig. 4. ESR Spectra of Argon Plasma-Induced Radicals of PBzMA, PST, and PMMA of Various Plasma Duration
Plasma conditions: 40 W, 0.5 Torr.

produced in argon plasma irradiated PBzMA together with the results obtained with PST,[7] a plasma-crosslinkable polymer and polymethyl methacrylate (PMMA),[8] a plasma-degradable polymer, with plasma irradiation time. As can be seen, the ESR spectrum of PBzMA is similar to that of plasma-irradiated PST when irradiated for a short time, but it gradually approaches the spectrum of plasma-irradiated PMMA as plasma irradiation time increases. This shows that PBzMA is a bifunctional polymer as expected from the viewpoint of the structure of the radical produced.

We earlier reported that the main components of the radicals constituting the ESR spectra of plasma-irradiated PST and plasma-irradiated PMMA are cyclohexadienyl-type and end-chain-type radicals, respectively as shown in Fig. 5, and that the former radicals cause a rapid crosslinking reaction involving an aromatic ring.[7,9]

We roughly estimated the structures of radicals produced on plasma-irradiated PBzMA, by approximating them to PST-type and PMMA-type radicals using a

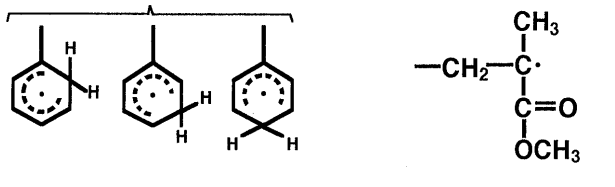

Fig. 5. Structures of Plasma-Induced Main Radicals in PST and PMMA

computer simulation of ESR spectra, in order to understand the composition ratio of cyclohexadienyl-type radicals and endchain-type radicals more quantitatively. The cyclohexadienyl-type radicals were produced preferentially, but the quantity produced gradually became constant with an increase in irradiation time and was overtaken by the quantity of endchain-type radicals produced (Fig. 6).

Figure 7 presents changes in the strength of cyclo-

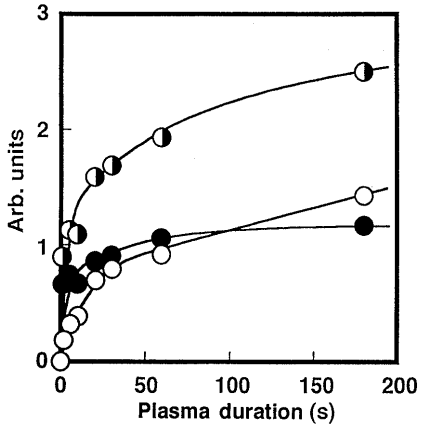

Fig. 6. Simulated Progressive Changes in Component Spectra of Plasma-Irradiated PBzMA Powder

Plasma conditions: 40 W, 0.5 Torr. ○, PMMA-type radical; ●, PST-type radical; ◑, total radicals.

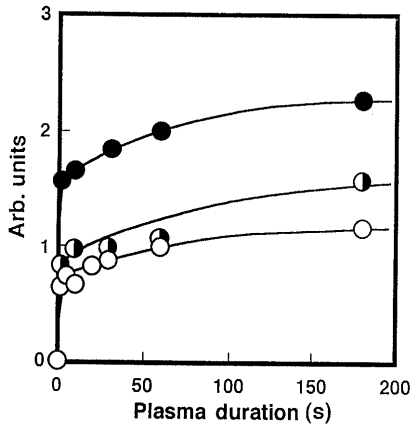

Fig. 7. Simulated Progressive Changes in PST-Type Radical Concentration of Each Plasma-Irradiated Bifunctional Polymer

Plasma conditions: 40 W, 0.5 Torr. ○, PBzMA; ●, PC; ◑, PET.

hexadienyl-type radicals deduced from the simulated spectra according to irradiation time together with PC and PET. When this figure is compared with the results of polymer degradation property in Fig. 3, it can be seen that the radical concentration is low with a polymer, of which degradation rate by argon plasma irradiation is low in all three polymers. That is, the low output of cyclohexadienyl-type radicals and the low polymer degradation rate of PBzMA suggest that a crosslinking reaction due to rapid radical recombination reaction is in progress.

Release Property of Theophylline from Plasma Irradiated Double-Compressed Tablets Containing Theophylline Using MMA-BzMA Copolymer as the Outer Layer PBzMA is thought to be transformed into a porous outer layer by oxygen plasma irradiation, since degradation of the polymer main chain and crosslinking reaction of the side chain proceeds with plasma irradiation causing changes in the radical structure, although an effectiveness equal to PC and PET cannot be expected. We first studied the release property of theophylline from an oxygen plasma irradiated double-compressed tablet containing theophylline with PBzMA in various amounts used for the outer layer. No theophylline was released from such a tablet containing PBzMA (100 mg) in an amount equivalent to PC and PET used for the outer layer as true of any plasma non-irradiated tablets; the release of only a small amount of theophylline was realized when the outer layer amount of PBzMA was decreased. These results suggest that an effective formation of micropores did not progress in homopolymer of PBzMA. This was also supported by SEM photographs of surface changes in the plasma-irradiated tablets. In order for micropores to be formed enabling the effective release of theophylline from double-compressed tablets in which PBzMA is used for the outer layer polymer, therefore, it is necessary to reduce the plasma crosslinking reaction and to give PBzMA the property of degradation and/or scattering by fragmentation. We therefore synthesized PBzMA copolymers of various composition ratios with PMMA, a typical degradable polymer, and prepared an oxygen plasma irradiated double-compressed tablet containing theophylline using those copolymers as the outer layer to study the release property of theophylline.

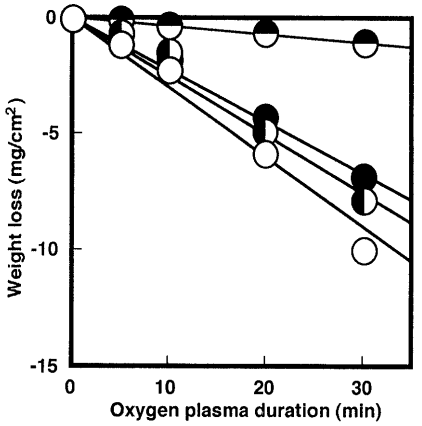

Fig. 8. Effect of BzMA Ratio on Plasma-Induced Degradation of MMA-BzMA Copolymer

Plasma conditions: 30 W, 0.5 Torr, O_2 50 ml/min. ○, PMMA; ◑, MMA: BzMA = 9 : 1; ●, MMA : BzMA = 4 : 1; ◓, PBzMA.

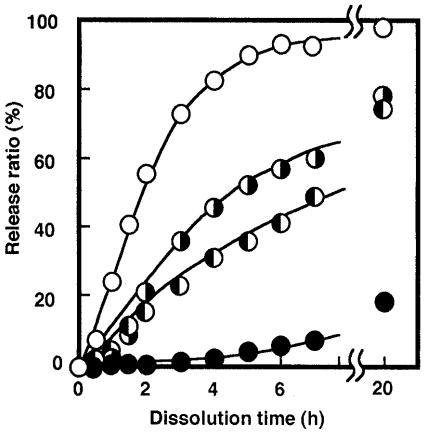

Fig. 9. Effect of BzMA Ratio in Copolymer on Dissolution Property of Theophylline from Plasma-Irradiated Double-Compressed Tablets

Outer layer: 100 mg. Plasma conditions: 30 W, 0.5 Torr, O_2 50 ml/min, 20 min. ○, PMMA; ◑, MMA : BzMA = 19 : 1; ◐, MMA : BzMA = 9 : 1; ●, MMA : BzMA = 4 : 1.

Figure 8 shows the influence of the composition ratio of MMA-BzMA copolymer in plasma degradation property of those copolymers. As is clear from Fig. 8, the plasma degradation property increased as expected with

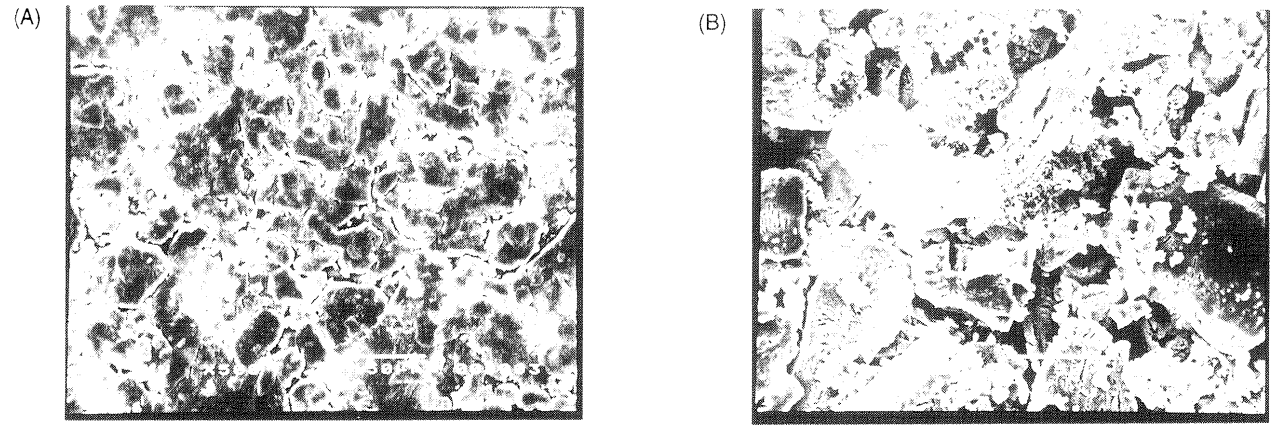

Fig. 10. Scanning Electron Photomicrographs of a Tablet Using a Copolymer of MMA:BzMA = 19:1 before (A) and after Oxygen Plasma-Irradiation (B)

Plasma conditions: 30 W, 0.5 Torr, O_2 50 ml·min, 20 min.

a decrease in the percentage of BzMA content, that is, a decrease in the percentage of content in the benzyl group in the copolymer.

Figure 9 shows results of the release of theophylline from the oxygen plasma irradiated double-compressed tablet containing theophylline using an MMA-BzMA copolymer for the outer layer. Theophylline release was not found from any non-plasma-irradiated tablets, but was found from the plasma-irradiated tablets. As shown, the release property becomes larger with decrease in the BzMA content in the copolymer. It has also been shown that theophylline release is possible with the BzMA content in the outer layer polymer of 20% or less, particularly under the conditions described in preparation of this tablet.

In Fig. 9 the release property of theophylline is good even where PMMA shown as the control has been used as a single outer layer polymer. However, that tablet was shown to be far more brittle in terms of strength and to disintegrate after the release of theophylline more quickly than the tablet in which a copolymer was used as the outer polymer.

With this plasma-irradiated tablet, the irradiation was performed at the output of 30 W over a duration of 20 min because theophylline release was the largest and disintegration of the tablet did not occur under those conditions, as shown by studies of various plasma irradiation conditions (output and duration of irradiation).

Also, it was confirmed by SEM photos that the release of theophylline from these tablets is the result of the effective formation of micropores. Figure 10 is a SEM photo of the surface of a non-plasma-irradiated tablet irradiated with oxygen plasma using a copolymer of MMA : BzMA = 19 : 1 as the outer layer at 30 W for 20 min. Deep micropores are formed on the entire particle in the plasma-irradiated tablet (B) as in the case of PC compared with the non-plasma-irradiated tablet (A). This has presumably made possible the drug release through these micropores in this double-compressed tablet in which a copolymer was used for the outer layer.

Conclusion

The results of measurements of ESR spectra showed that the plasma degradation reaction and plasma crosslinking reaction progress simultaneously on plasma irradiation of PBzMA. However, PBzMA having an aromatic ring on the side chain with a greater freedom showed greater plasma crosslinking reaction than bifunctional polymers such as PC and PET which have an aromatic ring on the main chain. Accordingly, the release of theophylline from the oxygen plasma-irradiated double-compressed tablet containing theophylline with PBzMA for a single outer layer was not satisfactory from the viewpoint of utility, even when a small amount of outer layer polymer was used.

If, however, a copolymer with plasma degradable polymers such as PMMA and PBzMA is used for the single outer layer, degradation and scattering of the polymer main chain are accelerated with a decrease in the percentage of the aromatic ring which plays an important role in the crosslinking reaction. This leads to an effective release of theophylline and at the same time makes it possible to control the release according to the composition ratio of the copolymer.

As described, the PBzMA copolymer is a new type polymer useful as a single polymer outer layer with a crosslinkable part on the side-chain, and can be applied to the construction of the DDS. This is expected to lead to new evolution in the development of controlled-release type DDS making use of plasma irradiation.

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