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A New Drug Delivery System Using Plasma-Irradiated Pharmaceutical Aids. VI. Controlled Release of Theophylline from Plasma-Irradiated Double-Compressed Tablet Composed of Water-Soluble Polymers as a Wall Material

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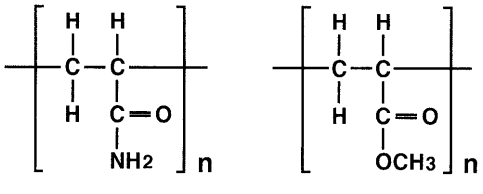
The rapid drug release from a double-compressed tablet containing theophylline with the water-soluble polymer polymethacrylic acid (PMAA) or polyacrylamide (PAAm) used as a wall material can be suppressed by argon plasma irradiation and changed into the slow release due to a decrease in the solubility of water-soluble polymers used as the outer layer. This report is the first to deal with an attempt to control the release of drugs by controlling polymer solubility, and to fabricate a completely soluble controlled release type of drug delivery system (DDS) making use of plasma processing.

Key words plasma processing; double-compressed tablet; theophylline; controlled-release; drug delivery system

In previous papers in this series on preparation of multilayered particles for use in a drug delivery system (DDS) with plasma processing[1–7] we have reported that novel controlled-release tablets can be obtained by oxygen plasma irradiation on the outermost layer of double-compressed tablets. These latter tablets are composed of theophylline as a core material and plasma-induced bifunctional (crosslinkable and degradable) polymers, polybenzylmethacrylate (PBzMA) and its copolymer with polymethylmethacrylate (PMMA) as a single wall material.[8]

When a water-soluble polymer is used as the wall material of the double-compressed tablet, the drug release rate from the tablet is dependent on the solubility of the polymer used. If, therefore, the polymer solubility is suppressed by the surface cross-linking reaction due to plasma irradiation, the drug release rate can be expected to be controlled depending on the solubility.

We previously reported that a relatively large amount of dangling bonds were produced in argon plasma irradiation on powder of water-soluble polymethacrylic acid (PMAA) as compared with other methacrylic polymers, and suggested that the cross-linking reaction occurred partially in PMAA although it is classified as a plasma degradable polymer.[9] On the other hand, polyacrylamide (PAAm), a water-soluble polymer, is well known to be one of the typical plasma cross-linkable polymers. Also, it is documented that the cross-linking reaction proceeds more predominantly in argon plasma irradiation free of oxidative decomposition than in oxygen plasma irradiation. On this basis, we studied the possibility of a rapid-release tablet being converted into a slow-release tablet in an experiment using argon plasma irradiation on a double-compressed tablet composed of water soluble polymers as a single wall material.



PMAA PAAm

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Experimental

Materials and Tablet Preparation Commercial monomer methacrylic acid (MAA)(Tokyo Kasei Co., Ltd., Japan) was purified before use by distillation. PMAA was prepared according to radical polymerization using an azobisisobutyronitrile as the radical initiator and was purified by dissolving it in methanol and precipitating in excess ethylether. Then it was dried *in vacuo* at 60 °C for 24 h and screened with a 200-mesh sieve. Mw = 1150000, Mn = 520000 and Mw/Mn = 2.20 were determined by gel permeation chromatography according to the method reported previously.[8] Commercial PAAm (Kishida Chemicals Co., Ltd., Japan) was purified repeatedly by dissolving it in water and precipitating in excess acetone. It was then dried *in vacuo* at 60 °C for 24 h and screened with a 200-mesh sieve. Mw = 1470000, Mn = 940000 and Mw/Mn = 1.57 were determined by the same method as for PMAA. Commercial theophylline (Nacalai Tesque Inc.) was dried *in vacuo* at 60 °C for 24 h, and used without further purification. Each tablet of PMAA and PAAm was obtained by compressing polymer powder (100 mg of the fractions screened through a 200-mesh sieve) into a flat-faced shape (13 mm in diameter) at a pressure of 200 kg/cm^2 for 30 s. The double-compressed tablets were obtained as follows: a flat-faced core theophylline tablet (10 mm in diameter) was first prepared at a pressure of 40 kg/cm^2 for 10 s, then the core tablet was placed onto half of the prescribed amount of powdered polymer as a wall material in a tablet die. After the rest of the powdered polymer was placed on the core tablet, the whole was compressed at pressure of 200 kg/cm^2 for 30 s. 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 The apparatus for plasma irradiation is essentially the same as reported earlier.[8] The plasma state was generated by use of radio frequency discharges of inductive coupling with supplied power of 30—50 W at 13.56 MHz. Flow volume (50 ml/min) and pressure of argon gas (0.5 Torr) for plasmolysis were controlled by changing evacuating speed. The sample tablets were placed on a glass-tripod in a reaction chamber to ensure homogeneous exposure to plasma gas.

Dissolution Test of Polymers The dissolution test of polymer tablets was conducted in distilled water by the standard dissolution method using a rotational basket apparatus (TR-5S3, Toyama Industry) at 37 ± 0.5 °C with 100 rpm. Tablet dissolution was determined by difference between the weights before and after dissolution.

Test of Theophylline Release Test of theophylline release from the double-compressed tablets was conducted in distilled water, according

to the standard dissolution method using a rotational basket apparatus at 37±0.5 °C with 100 rpm.[8] Released theophylline was periodically assayed by UV absorption spectrum (UV-3100DS, Shimadzu Co.) at the wavelength of 270 nm.

Results and Discussion

Changes in Dissolution of Water-Soluble Polymers, PMAA and PAAm, with Argon Plasma Irradiation We measured changes in the solubility of these water-soluble polymers by argon plasma on the compressed tablets of PMAA and PAAm.

Figure 1 illustrates the dependence of changes in the rate of dissolution on the plasma irradiation time when argon plasma was irradiated at the output of 30 W on the compressed PMAA tablet.

As is clear in the figure, PMMA dissolution rate decreased with plasma irradiation time due to the surface cross-linking reaction.[9] However, the dissolution curves after plasma irradiation for 5 and 10 min clearly show that the effect of the plasma irradiation time tended to decrease slowly. This is probably because the decomposition reaction in PMAA occurs in spite of the progress of the cross-linking reaction. Thus, the production of the surface cross-linking layer is levelled-off and ceases to increase even with an increase in the plasma irradiation time.

PAAm, a plasma-crosslinkable polymer, is thought to have a greater plasma irradiation effect on the changes in the dissolution than PMAA. Figure 2 shows the dependence of change in dissolution rate on plasma irradiation time when argon plasma was irradiated at the output of 30 W on the compressed PAAm tablet.

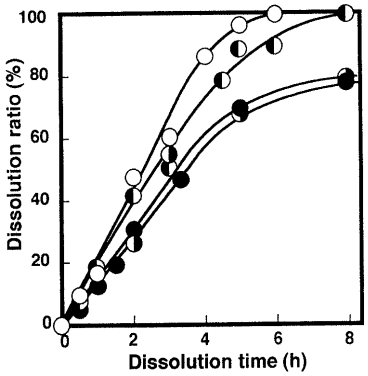

Fig. 1. Effect of Plasma-Duration on Dissolution Ratio of PMAA

Plasma conditions: 30 W, 0.5 Torr, Ar 50 ml/min. ○, blank; ◐, 3 min duration; ●, 5 min duration; ◑, 10 min duration.

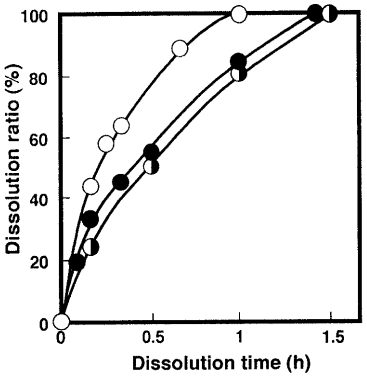

Fig. 2. Effect of Plasma-Duration on Dissolution Ratio of PAAm

Plasma conditions: 30 W, 0.5 Torr, Ar 50 ml/min. ○, blank; ●, 5 min duration; ◑, 10 min duration.

As shown, the rate of solubility of PAAm decreased with plasma irradiation time. However, the rate of decrease was not as much as expected, probably because the solubility of PAAm under the conditions of this test (in distilled water) is higher than PMAA.

So, if the output power of plasma irradiation is raised, a thicker surface cross-linking layer will be formed and a further decline in the solubility of PAAm can be expected. Then, we studied changes in the dissolution using a higher output power of plasma irradiation. Figure 3 shows the dependence of the changes on plasma irradiation output.

A marked decline in the rate of dissolution was observed as expected at the plasma output power of 50 W.

Theophylline Release from Plasma-Irradiated Double-Compressed Tablets Composed of Theophylline with Water-Soluble Polymers, PMAA and PAAm, as a Wall Material Figure 4 illustrates the dependence of the release property of theophylline from the double-compressed tablet composed of theophylline with PMAA as a wall material on the plasma irradiation time.

The rate of release of theophylline is markedly lower than that of the non-plasma-irradiated tablet. The dependence of the rate of dissolution from the double-compressed tablet was consistent with that of the compressed PMAA tablet (Fig. 1), and not much difference

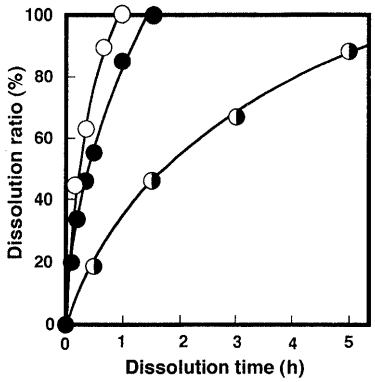

Fig. 3. Effect of Plasma-Power on Dissolution Ratio of PAAm

Plasma conditions: 0.5 Torr, Ar 50 ml/min, 5 min duration. ○, blank; ●, 30 W; ◑, 50 W.

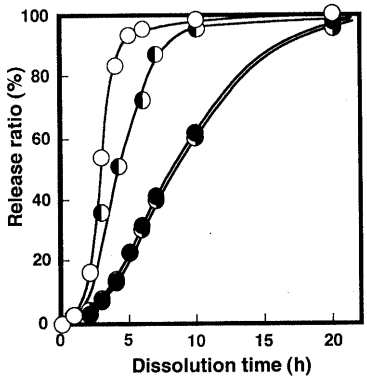

Fig. 4. Effect of Plasma-Duration on Dissolution Properties of Theophylline from Double-Compressed Tablet Composed of PMAA as a Wall Material

Plasma conditions: 30 W, 0.5 Torr, Ar 50 ml/min. Outer layer: PMAA (100 mg). ○, blank; ◐, 3 min duration; ●, 5 min duration; ◑, 10 min duration.

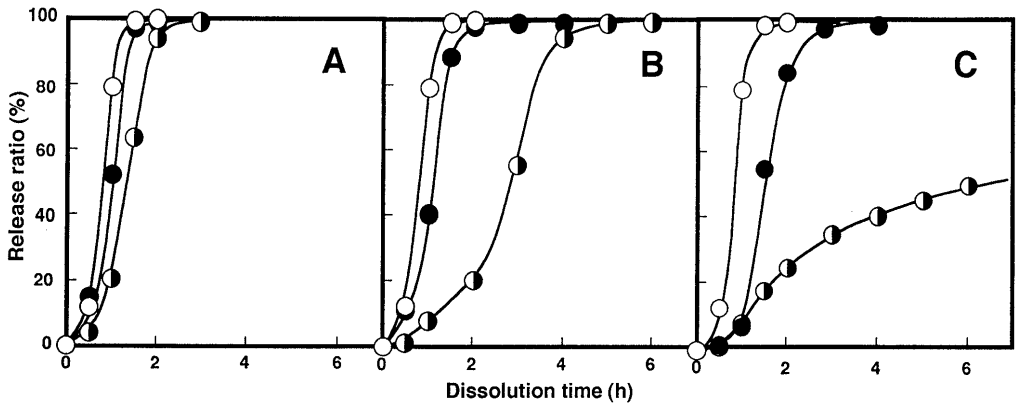

Fig. 5. Effect of Plasma-Irradiation under Various Operational Conditions on Dissolution Properties of Theophylline from Double-Compressed Tablet Composed of PAAm as a Wall Material

Plasma conditions: (A) 30 W, 0.5 Torr, Ar 50 ml/min; (B) 40 W, 0.5 Torr, Ar 50 ml/min; (C) 50 W, 0.5 Torr, Ar 50 ml/min. Outer layer: PAAm (100 mg). ○, blank; ●, 5 min duration; ◑, 10 min duration.

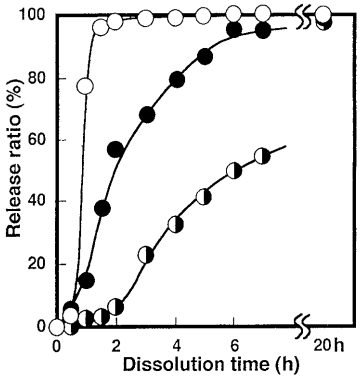

Fig. 6. Effect of Plasma-Irradiation on Dissolution Properties of Theophylline from Double Compressed Tablet Composed of a Larger Amount of PAAm as a Wall Material

Plasma conditions: 50 W, 0.5 Torr, Ar 50 ml/min. Outer layer: PAAm (150 mg). ○, blank; ●, 5 min duration; ◑, 10 min duration.

in the rate of theophylline release was found between plasma duration of 5 and 10 min.

Likewise, Fig. 5 shows the dependence of the theophylline release property from the double-compressed tablet with PAAm as a wall material on the various plasma durations at the plasma irradiation output of 30W (A), 40W (B) and 50W (C).

Theophylline release decreased with plasma duration at any output (A, B, C). However, since the rate of dissolution of PAAm under the conditions of this dissolution test (distilled water) was very high compared with PMAA (*vide supra*), the theophylline release at an output power of 30 W was still rapid. This release, however, depends heavily on the plasma irradiation output as shown in Figs. 5B and 5C, and markedly slow release is noted at the output of 50 W (C) with plasma duration of 10 min. This slow release behavior of theophylline corresponds well with the changes in dissolution of PAAm and so is believed due to the decline in PAAm solubility.

The release property of a drug from the plasma-irradiated double-compressed tablet is thought to depend not only on the conditions of plasma irradiation but also on the conditions of tablet preparation.

In fact, when the amount of PAAm as a wall material was increased from 100 to 150 mg in a plasma-irradiated double-compressed tablet, a further decrease in the rate of theophylline release was clearly shown with changes in the release pattern (Fig. 6).

In SEM photographs taken of the double-compressed tablets before and after plasma irradiation we also saw no significant difference. Each plasma-irradiated double-compressed tablet dissolved slowly in water and swelled as did the non-plasma-irradiated tablet, and dissolved completely without any residue after the dissolution test. Thus, as illustrated in Fig. 7, the completely soluble sustained-release systems (B) reported herein should be considered distinct in nature from those we have previously reported (A),[1-8] where the insoluble outer layer simply changed into a porous layer.

Conclusion

We have thus far reported a series of developments of drug release control type DDS and obvious advantages for preparing them making use of plasma irradiation.[1-8] However, the DDS previously reported relates to a method for controlling the drug release (conversion from a non-release tablet to a controlled-release tablet) by oxygen plasma irradiation onto a double-compressed tablet. This converts the polymer layer used as a wall material into the porous outer layer, thereby giving the release property to the tablet, and the polymer layer remains as residue after the completion of drug release.[1-8]

The present report has shown that rapid drug release from the double-compressed tablet containing theophylline with a water-soluble polymer used as a wall material can be suppressed by argon plasma irradiation and changed into a slow release.

From the viewpoint of research in the field of plasma chemistry, attempts to control and prevent the elution of low molecular weight substances in insoluble polymer by the plasma-induced crosslinking reaction have been reported.[10] The present report, however is the first to deal with an attempt to control the release of the eluate by controlling polymer solubility. The completely soluble controlled release type of DDS using plasma processing reported here is expected to be developed to serve extensive

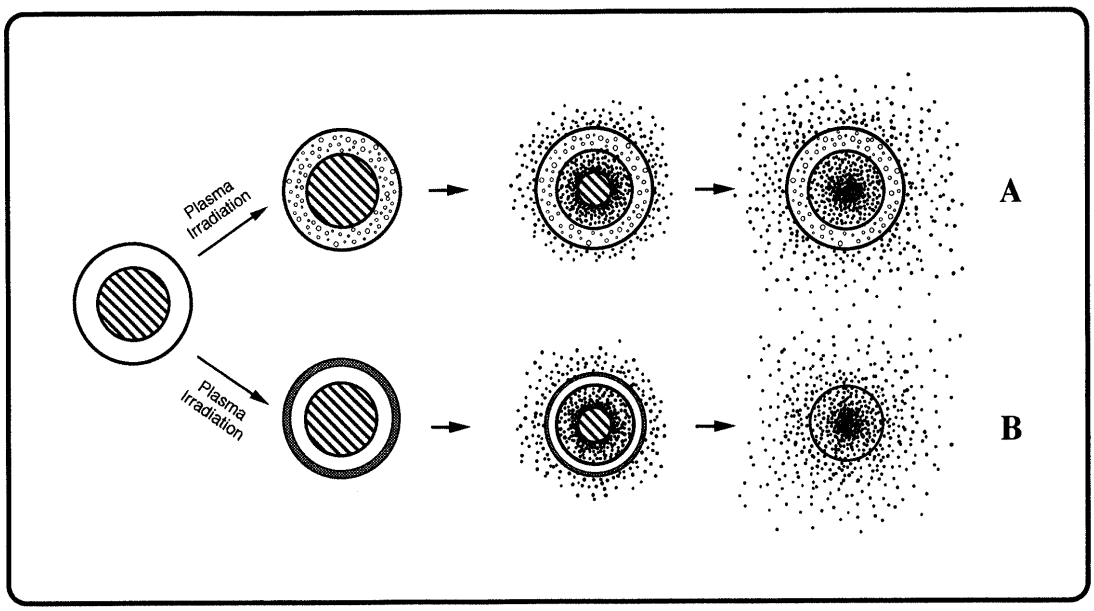

Fig. 7. Schematic Representation for Two Types of Sustained-Release Systems for Drug Delivery of Reservoir System

uses and purposes including possible application to oral administration.

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