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A New Drug Delivery System (DDS) Development Using Plasma-Irradiated Pharmaceutical Aids. IV. Controlled Release of Theophylline from Plasma-Irradiated Double-Compressed Tablet Composed of Polycarbonate as a Single Wall Material

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A controlled-release tablet can be obtained by oxygen plasma irradiation on the outer layer double-compressed tablets prepared from theophylline as a core material and polycarbonate derived from bisphenol A (PC) as a single wall material, making this possible that PC is of intramolecular bifunctionality, crosslinkable phenyl group and degradable carbonate group 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 manufacturing as well as plasma operational conditions.

Keywords plasma irradiation; double-compressed tablet; controlled release; polycarbonate; DDS; ESR

As part of our continuing work on plasma chemistry and its application in the development of new pharmaceutically useful materials,[1-4] we have recently reported preparation of multilayered particles applicable for drug delivery system (DDS) using plasma processing (Fig. 1). 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 prepared from theophylline as a core material and a mixture of plasma degradable polyoxymethylene (POM) and plasma-crosslinkable polystyrene (PST) as a wall material.[2] The work has further been extended to preparation of the controlled release tablet by using bioerodible polylactic acid (PLA) in place of PST.[3]

In order to understand the nature of plasma treatment, we have conducted a number of plasma irradiations on a wide variety of polymers, synthetic and natural, and the structure of surface radicals formed was elucidated by ESR (electron spin resonance) spectral measurements coupled with systematic computer simulations.[5-18] Based on a series of this work, we were able to establish the general relationship between the structure of radicals formed and the nature of polymer degradation (etching) as an effect of plasma irradiation.

In this paper, we examined controlled-release tablets prepared from theophylline as a core material and bioerodible polycarbonate derived from bisphenol A (PC) as a single wall material, since the polycarbonate is considered to be of intramolecular bifunctionality, crosslinkable phenyl group and degradable carbonate group, as a plasma irradiation effect. The controlled-release tablets were obtained by oxygen plasma irradiation on the outer layer of the above-mentioned double-compressed tablet, so as to cause release of theophylline at different rates depending on plasma operational conditions and tablet manufacturing.

Experimental

Materials and Tablet Preparation Commercial PC derived from bisphenol A (Aldrich) (Fig. 2) was purified by dissolving it (3 g) in chloroform (120 ml) and precipitating in excess methanol (3 l). Then, the PC was pulverized and screened through prescribed mesh sieves. These powdered materials were dried *in vacuo* at 60 °C for 1 d before use. The molecular weight of PC powder thus obtained was number-average molecular weight ($\bar{M}n$) = 23000, weight-average molecular weight ($\bar{M}w$) = 47000 ($\bar{M}w/\bar{M}n = 2.04$) based on the calibration of standard polystyrene, which was determined by gel permeation chromatography (GPC) (Shimadzu LC-6A), equipped with gel column (GPCKF-800p, GPC KF-80 m) at 40 °C, and refractive index (RI) detector (Shimadzu, RID-6A) in THF as an elution solvent.

Commercial theophylline was dried *in vacuo* at 60 °C for 1 d, and used without further purification. PC tablets were obtained by compressing

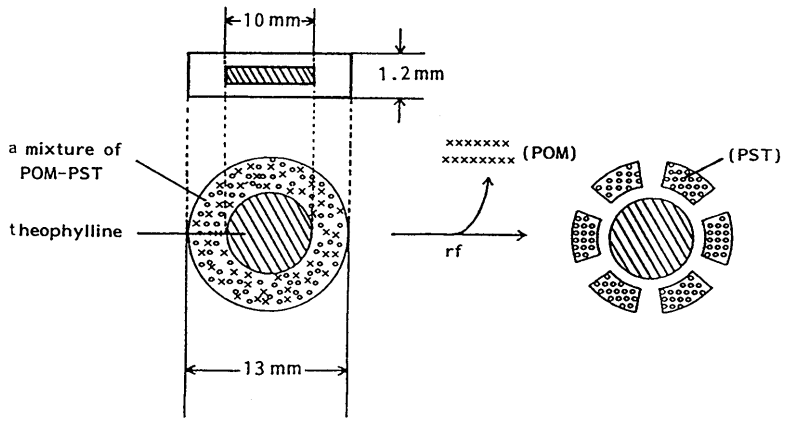


Fig. 1. Schematic Representation for Preparation of Double-Compressed Tablet with Porous Outer Layer Induced by Plasma Irradiation

PC 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. Likewise, the double-compressed tablets were prepared at pressure of 100 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 PC as a wall material. All flat-faced tablets were prepared using a hand press instrument (SSP-10A, Shimadzu Co.) in a tablet die (P/N202-32010, Shimadzu Co.).

Plasma Irradiation Schematic representation of the apparatus for plasma irradiation is shown in Fig. 3, and is essentially the same as reported earlier.[2] The plasma state was generated by use of radio frequency (rf) discharges of inductive coupling with supplied power of 30—50 W at 13.56 MHz. Flow volume (50 ml/min) and pressure of oxygen 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.

Degradation rate of PC tablets induced by plasma irradiation was determined by measurement of the weight loss at various stages of plasma duration.

ESR Spectral Measurement Powdered PC samples, 50 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 with stirring of samples 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.[8]

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, as previously.[21] Released theophylline was periodically assayed by UV absorption spectrum at the wavelength of 270 nm.

Results and Discussion

Degradation of PC We first examined the degradation of PC by the oxygen plasma irradiation under a set of operational conditions. The rate of degradation is shown in Fig. 4, together with those of polystyrene (PST) (0.04 mg/cm^2/min) and polymethylmethacrylate (PMMA) (0.75 mg/cm^2/min) for comparison. It is seen that each polymer degradation is proportional to the plasma duration, and degradation rate of PC (0.11 mg/cm^2/min) is relatively low, compared with that of typical plasma-degradable PMMA,[2] despite the fact that PC is of plasma-degradable carbonate groups in the polymer main chain.

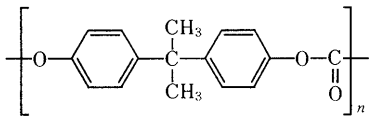


Fig. 2. Structure of Polycarbonate Derived from Bisphenol A

Figure 5 shows the effect of oxygen plasma-supplied power on degradation of PC. It is clear that the degradation rate increases as the power increases, indicating that degradation rate of PC can be easily controlled by the plasma-supplied power.

Examination of argon plasma irradiation has also shown the degradation of PC, but the effect is much lower than that by oxygen plasma; thus the difference in the degradation rate among the polymers examined is small as in the case among other types of polymers.[2,3] This indicates that polymers are generally more prone to undergo the surface crosslink reactions than degradation with argon plasma irradiation, due to the absence of oxidative decomposition with oxygen plasma irradiation.

ESR Spectra of Argon Plasma-Irradiated PC To obtain further insight into the nature of plasma-induced PC degradation, the PC radicals formed by argon plasma irradiation were studied by ESR. Progressive changes in the room temperature ESR spectra with various plasma durations are shown in Fig. 6, together with those of PST for a comparison. The gross features of the spectra are similar to each other, and composed mainly of apparent triplet peaks in both cases. The observed ESR spectra are nicely reproduced by the simulated spectra shown as dotted lines.

We have already undertaken plasma irradiations on various polycondensed polymers including polyethylene-terephthalate (PET) and polyimide (PI), and the radicals

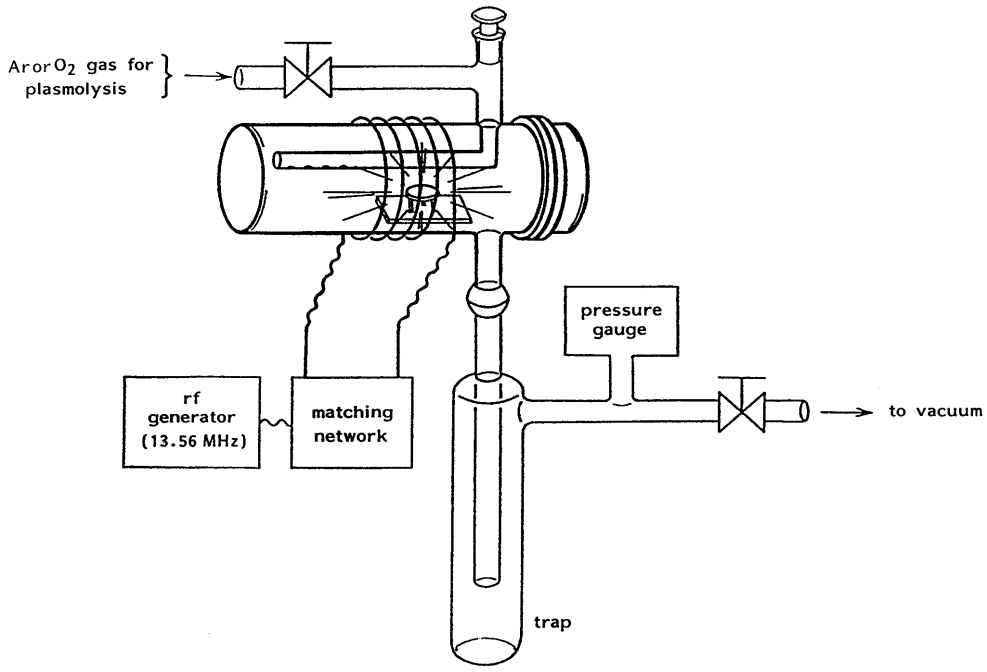


Fig. 3. Schematic Representation for Preparation of Plasma-Irradiated Tablet

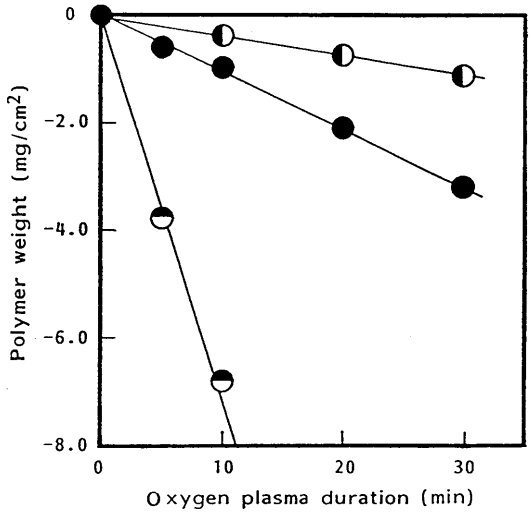


Fig. 4. Effect of Oxygen Plasma Irradiation on Polymer Degradation

◐, polystyrene (PST); ●, polycarbonate (PC); ◓, polymethylmethacrylate (PMMA). Plasma operational conditions; supplied power, 50 W; pressure, 0.5 Torr; flow rate of oxygen gas, 50 ml/min.

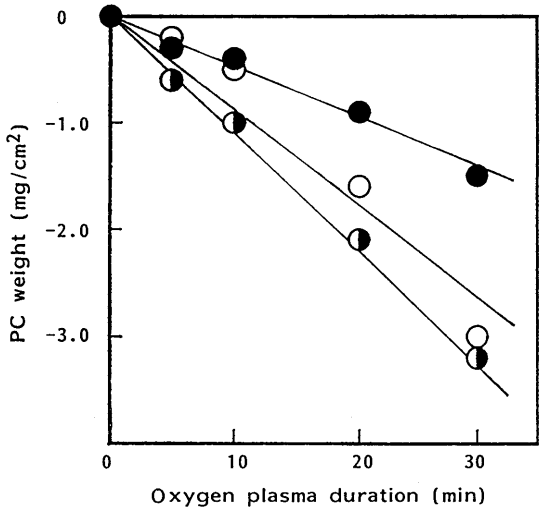


Fig. 5. Effect of Plasma-Supplied Power (W) on PC Degradation

●, 30 W; ○, 40 W; ◑, 50 W. Plasma operational conditions: pressure, 0.5 Torr; flow rate of oxygen gas, 50 ml/min.

formed were studied by ESR with the aid of systematic computer simulations. The details will be reported in a separate paper dealing only with that subject, but the sense of the results on PC can be briefly mentioned here: It was found from the computer simulations that the major triplet spectra are derived from cyclohexadienyl-type radicals formed by nearly random addition of a hydrogen atom to the three positions on the aromatic ring of PC. The observed spectra are contaminated, in addition to the triplet, with a small amount of dangling bond sites (DBS) represented by a broad single line as in the case of PST. Thus, the progressive changes in the spectral pattern are found to stem from increase in the ratio of DBS in the radicals formed.

We recently demonstrated that cyclohexadienyl-type radicals formed in plasma-irradiated PST have a great tendency to undergo the radical recombination resulting in the formation of the crosslinked surface layers.[3,7] Therefore, it can be reasonably assumed that PC also readily

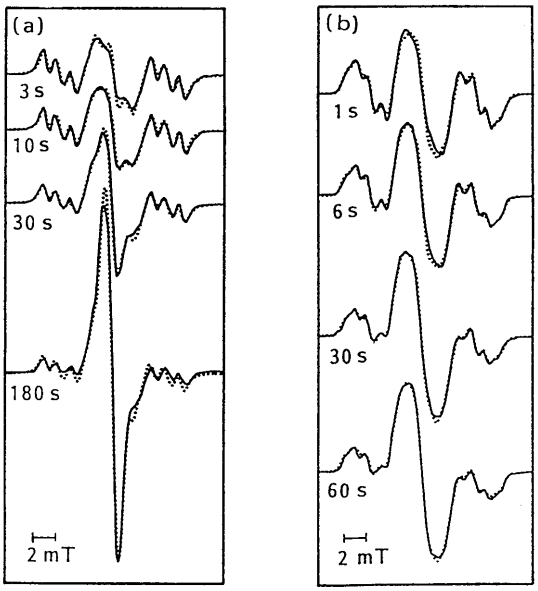


Fig. 6. Observed and Simulated ESR Spectra of Argon Plasma-Induced Radicals of PC (a) and PST (b) with Various Plasma Durations

The simulated spectra are shown as dotted lines.

undergoes the crosslink reactions with plasma irradiation on the basis of the ESR spectra being similar to those of PST, as well as a concurrent polymer mainchain scission by decomposition of carbonate groups.

Effect of Plasma Operational Conditions on Dissolution Properties of Theophylline We examined the effect of various plasma operational conditions on dissolution properties of theophylline from the double-compressed tablets.

Figure 7 shows the effect of plasma duration on these properties from the plasma-irradiated double-compressed tablet with 40 and 50 W of supplied power.

Theophylline was released from all the plasma-irradiated tablets, while little was released from any of the non-plasma-irradiated tablets (blank) within dissolution time examined (23 h). This, as well as the results reported earlier,[2-4] indicates that theophylline was released from the micropores formed on the outer layer as a result of the combined reactions of degradation and crosslinkage in PC molecules. It is also seen that the dissolution rate of theophylline increases nicely, as the plasma duration increases when 40 W of plasma-supplied power was employed. However, this is not the case with 50 W, where there is no relationship between the dissolution rate and plasma duration. The dissolution rate is the highest with plasma irradiation for 5 min and the lowest for 7 min, even though the tablet weight loss due to PC degradation increases proportionally to the plasma duration. We note that the dissolution rate of theophylline from the tablet argon plasma-irradiated was much lower than that from oxygen plasma-irradiated tablet under the same plasma operational conditions. This is consistent with the result of PC degradation described above.

Thus, the present result indicates that the importance of choosing the optimal plasma operational conditions to achieve the desired dissolution rate of drug.

Effect of the Set of Conditions Chosen for Tablet Manufacturing on Dissolution Properties of Theophylline Figure 8

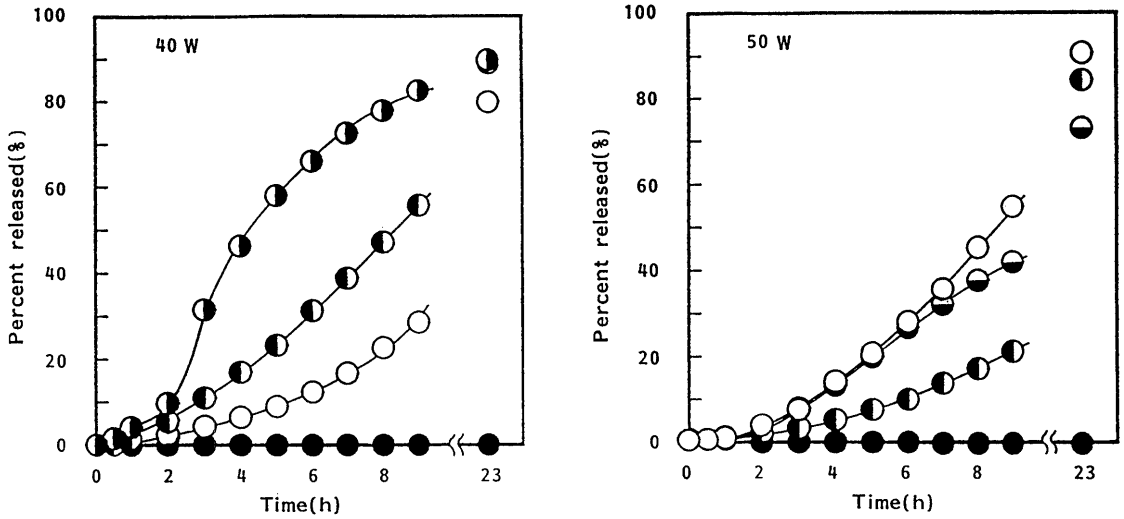


Fig. 7. Effect of Plasma-Duration on Dissolution Properties of Theophylline from the Double-Compressed Tablets (100 mg of PC Powder <200 Mesh Sieve) under Plasma-Supplied Power of 40 W and 50 W

◒, 4 min (weight loss; 2.5 mg for 50 W); ○, 5 min (weight loss; 3.5 mg for 40 W, 3.9 mg for 50 W); ◐, 7 min (weight loss; 4.3 mg for 40 W, 5.9 mg for 50 W); ◑, 10 min (weight loss; 6.9 mg for 40 W); ●, blank. Plasma operational conditions: pressure, 0.5 Torr; flow rate of oxygen gas, 50 ml/min.

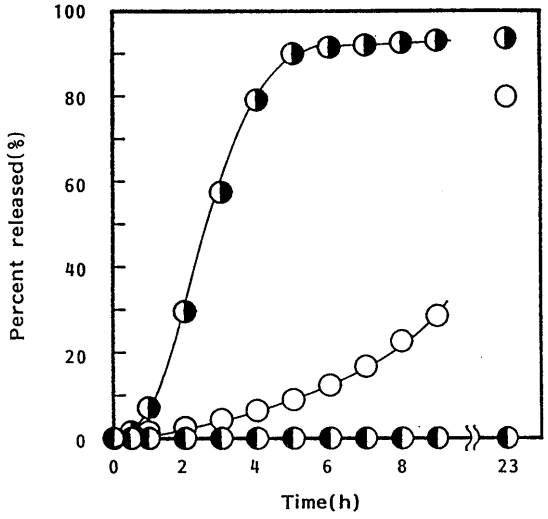


Fig. 8. Effect of Weight of the PC in Outer Layer of Double-Compressed Tablet on Dissolution Properties of Theophylline

◑, 80 mg (4.2 mg); ○, 100 mg (3.5 mg); ◐, 120 mg (2.4 mg). Plasma operational conditions: plasma duration, 5 min; supplied power, 40 W; pressure, 0.5 Torr; flow rate of oxygen gas, 50 ml/min.

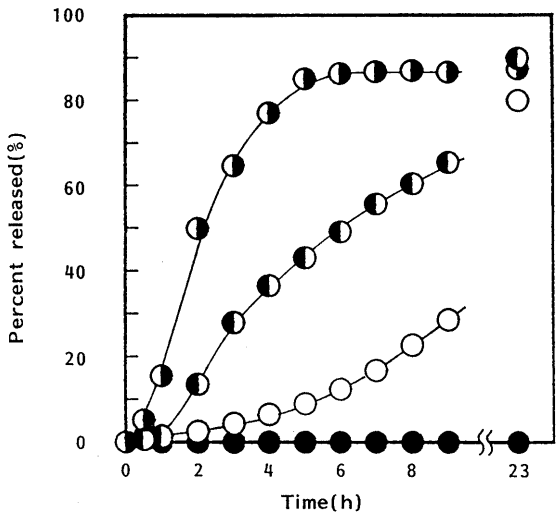


Fig. 9. Effect of Particle Size of PC Powder in the Outer Layer on Dissolution Properties of Theophylline

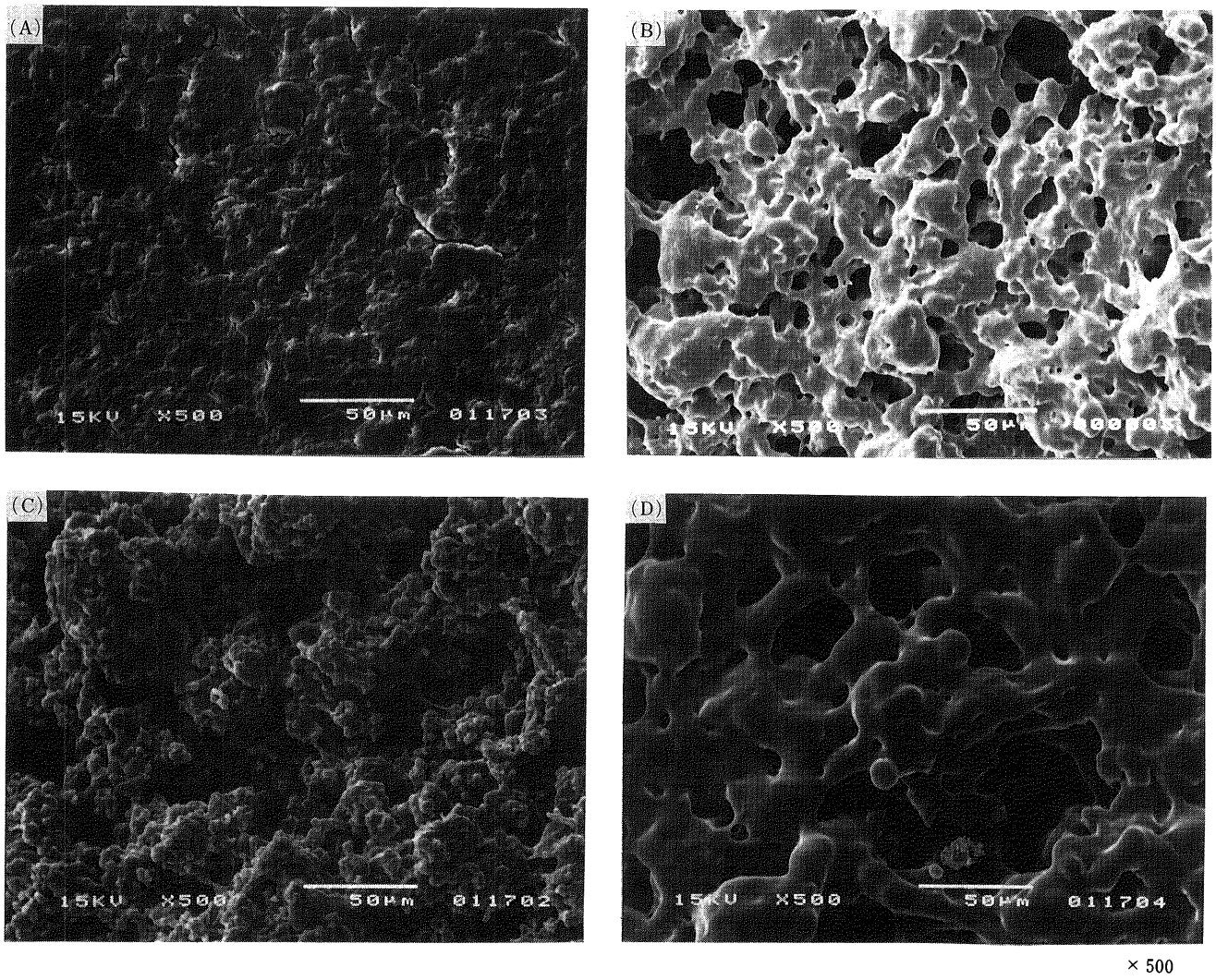
PC in outer layer: 100 mg. ◑, 100—140 mesh (7.0 mg); ◐, 140—200 mesh (4.2 mg); ○, <200 mesh (3.5 mg); ●, blank. Plasma operational conditions: plasma duration, 5 min; supplied power, 40 W; pressure, 0.5 Torr; flow rate of oxygen gas, 50 ml/min.

shows the effect of PC amount in preparation of double compressed tablet on the dissolution of theophylline; the effect is apparently related to thickness of the outer layer. The dissolution rate appears to be inversely proportional to the thickness of the outer layer, as expected.

One noteworthy feature, however, is that the smaller the amount of PC used, the greater was the weight loss observed. This is rather unexpected since we employed the identical plasma operational conditions in all cases. Although we can present no convincing evidence at present, we believe that the thermal effect of the plasma is greater on the smaller tablet and facilitates the PC degradation.

Examination of the dependence of particle size of PC powder on the theophylline dissolution (Fig. 9) showed the dissolution rate to be markedly affected by PC particle size under the plasma operational conditions used. The dissolution rate as well as the PC weight loss clearly increases as the particle size of PC increases. Since one of the characteristics of plasma irradiation is that it is surface-limited, the effect of PC particle size on the dissolution rate (and PC weight loss) may be attributed to the high porosity of the outer layer of the tablet prepared with larger particles of PC; such a tablet then has a greater surface area exposed to plasma gas. If such is the case, plasma-glow may be able to penetrate to the area of the core theophylline and decompose part of the theophylline. In fact, theophylline release from the tablet using 100—140 mesh PC levelled off in a rather short period of dissolution period (with in 5 h) with less than 90% of release (Fig. 9).

Scanning Electron Microscopy (SEM) The surface characteristics of the plasma-irradiated tablet were examined by SEM (JEOL, JSM T-330A). Figure 10 shows several SEM photographs of the surface of double-compressed tablets before and after oxygen plasma-



× 500

Fig. 10. Scanning Electron Photomicrographs of the Double-Compressed-Tablet Before and After Oxygen Plasma Irradiation

(A) Blank, 100 kg/cm^2, 30 s. (B) 40 W, 0.5 Torr, O_2 50 ml/min, plasma duration for 10 min. (C) 40 W, 0.5 Torr, O_2 50 ml/min, plasma duration for 5 min. (D) 50 W, 0.5 Torr, O_2 50 ml/min, plasma duration for 5 min. PC in outer layer: 100 mg (< 200 mesh).

irradiation. Tablet surface has taken on very rough structure with plasma irradiation at 40 W for 5 min, in comparison with that of the blank tablet, and a number of micropores are nicely formed on the tablet surface plasma-irradiated with 40 W for 10 min.

It should be noted that, although we do not show the SEM photograph, the tablet surface of argon plasma-irradiated under otherwise identical conditions did not produce the surface roughness to as great as that by oxygen plasma irradiation.

On the other hand, with plasma irradiation at 50 W for 5 min, although the micropores were formed, the PC surface of the tablet apparently softened and/or melted as a result of the thermal effect of plasma; this may have caused part of the resulting micropores to become clogged and their number to be reduced, accounting for the retardation of theophylline dissolution with a longer plasma irradiation under this power (Fig. 7).

Thermal Effect on Dissolution Properties of Theophylline Finally, in order to scrutinize whether or not the micropores are efficiently formed by plasma irradiation other than having an thermal effect, we undertook heating experiments of the double-compressed tablet in an oxygen atmosphere. The heating temperatures chosen were 160 and 180 °C, since the glass transition temperature (T_g) of PC in 149 °C. The dissolution profiles of the double-compressed tablets heated at these temperature for 30 min are shown in Fig. 11. Theophylline was released, though in small quantity, by simple heat-treatment of the tablet without plasma irradiation, at similar dissolution rates at both temperatures. This indicates that the PC was partially decomposed under the present conditions of heat-treatment. Heat-treatment at less than 160 °C did not cause the release of theophylline to any appreciable extent.

The SEM photograph of the double-compressed tablet after heat treatment showed that the outer layer of PC converted to a porous structure, but at the same time the surface of the tablet melted, superficially similar to the case of plasma irradiation at higher power. However, heat-treatment of the tablet caused the bulk layer of PC to melt, so that one cannot expect the formation of the microporous structure to be as effective as plasma irradiation. In fact, the final released-percent of theophylline even after prolonged dissolution time (23 h) was only *ca.* 50—70% (Fig. 11). This is in sharp contrast to the percentage from plasma-irradiated tablets, which was more than 90% in

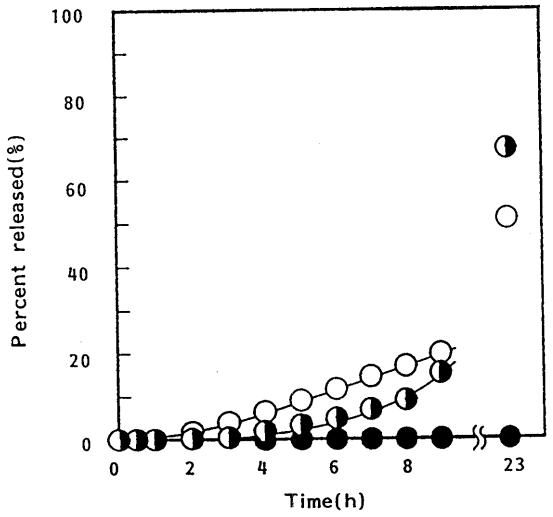


Fig. 11. Effect of Heat-Treatment of the Double-Compressed Tablet for 30 min at a 50 ml/min Flow Rate of Oxygen Gas on Dissolution Properties of Theophylline

PC in outer layer: 100 mg (<200 mesh). ○, 160 °C (1.9 mg); ◑, 180 °C (5.9 mg); ●, blank.

most cases. Heat treatment should thus be considered distinct in nature from the effect of plasma irradiation.

Conclusion

Oxygen plasma irradiation on double-compressed tablets prepared from a smaller theophylline tablet as a core material and PC powder as a single wall material caused formation of a porous structure of PC on the outer layer of the tablet. This occurred because polymers prepared by polycondensation such as PC are of intramolecular bifunctionality, plasma-crosslinkable and plasma-degradable as an effect of plasma irradiation.

As a result, the dissolution profiles can be varied so as to allow release of theophylline at different rates, depending on the set of conditions chosen for tablet manufacturing and plasma operational conditions. SEM findings of the tablet surface clearly indicated that theophylline was released from the tablet through the resulting micropores.

It is hoped that further devices applicable to a wide range of drugs and polymers will be developed in the course of work now in progress to examine the usefulness of plasma irradiation for DDS fabrications.

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References

1) M. Kuzuya, *Hyomen*, **27**, 885 (1989).
2) M. Kuzuya, A. Noguchi, H. Ito, M. Ishikawa, *DDS*, **6**, 119 (1991).
3) M. Kuzuya, H. Ito, N. Noda, I. Yamakawa, S. Watanabe, *DDS*, **6**, 437 (1991).
4) I. Yamakawa, S. Watanabe, Y. Matsuno, M. Kuzuya, *Biol. Pharm. Bull.*, **16**, 182 (1993).
5) For review, see M. Kuzuya, *J. Photopolym. Sci. Technol.*, **5**, 407 (1992).
6) M. Kuzuya, A. Koide, A. Ito, A. Noguchi, *Chem. Lett.*, **1989**, 555.
7) M. Kuzuya, A. Noguchi, H. Ito, S. Kondo, N. Noda, *J. Polym. Sci. Polym., Chem.*, **29**, 1 (1991).
8) M. Kuzuya, A. Noguchi, M. Ishikawa, A. Koide, K. Sawada, A. Ito, N. Noda, *J. Phys. Chem.*, **95**, 2398 (1991).
9) M. Kuzuya, M. Ishikawa, A. Noguchi, H. Ito, K. Kamiya, T. Kawaguchi, *J. Mater. Chem.*, **1**, 387 (1991).
10) M. Kuzuya, H. Ito, S. Kondo, N. Noda, A. Noguchi, *Macromolecules*, **24**, 6612 (1991).
11) M. Kuzuya, K. Kamiya, K. Sawada, *Proc. Jpn. Sym. Plasma Chem.*, **4**, 317 (1991).
12) For review, see M. Kuzuya, "Trends in Physical Chemistry," Vol. 2, Council of Science Research Integration, India, 1991, pp. 39—63.
13) M. Kuzuya, M. Ishikawa, A. Noguchi, K. Sawada, S. Kondo, *J. Polym. Sci. Polym. Chem.*, **30**, 379 (1992).
14) M. Kuzuya, N. Noda, S. Kondo, K. Washino, A. Noguchi, *J. Am. Chem. Soc.*, **114**, 6505 (1992).
15) M. Kuzuya, S. Kondo, H. Ito, A. Noguchi, *Appl. Surf. Sci.*, **60/61**, 416 (1992).
16) M. Kuzuya, K. Sawada, T. Takai, A. Noguchi, *Polymer J.*, **25**, 75 (1993).
17) M. Kuzuya, K. Kamiya, Y. Yanagihara, Y. Matsuno, *Plasma Source Sci. Technol.*, **2**, 51 (1993).
18) M. Kuzuya, J. Niwa, H. Ito, *Macromolecules*, **26**, 1990 (1993).