# A New Drug Delivery System Using Plasma-Irradiated Pharmaceutical Aids. IX. Controlled-Release of Theophylline from Double-Compressed Tablet Composed of Cellulose Derivatives as Wall Material

Kousuke ITO, Shin-ichi KONDO, and Masayuki KUZUYA*

*Laboratory of Pharmaceutical Physical Chemistry, Gifu Pharmaceutical University, 5–6–1 Mitahora-Higashi, Gifu 502–8585, Japan.* Received August 15, 2001; accepted September 25, 2001

**The rapid release from a double-compressed tablet containing theophylline with the water-soluble polymer, hydroxypropylmethylcellulose (HPMC) or hydroxypropylmethylcellulose phthalate (HPMCP), used as a wall material can be suppressed by argon plasma-irradiation and changed into the sustained-release system due to a decrease in solubility of the outer layer. It was shown that the release profiles can be varied so as to cause theophylline release at different rates, depending on the set of conditions chosen for tablet manufacture and for plasma operation.**

**Key words** plasma technique; ESR; double-compressed tablet; cellulose derivative; sustained-release

In a series on preparation of double-compressed tablets for use in a drug delivery system (DDS) with plasma techniques,[1,2] we have reported that novel sustained- and delayed-release tablets can be obtained by argon plasma-irradiation on the outer layer of double-compressed tablets. These tablets used theophylline as a core material and the outer layer polymers being practically used as pharmaceutical aids such as Eudragits L100, S100 and L100-55 in a previous paper.[3]

It is well known that derivatization of cellulose can readily change its physicochemical property and its functions of cellulose. Thus, there are a number of cellulose derivatives industrially used as pharmaceutical aids [17 derivatives in Japan Pharmacopoeia (JP) XIII] such as methylcellulose (MC, as binder, film coating materials), ethylcellulose (EC as film coating materials), hydroxypropylcellulose (HPC as binder, film coating materials), carboxymethylcellulose (CMC as disintegrants) and so on, several of which have been studied on the nature of plasma-induced radical formation,[4—7] including the mechanoradicals of cellulose and amylose.[8] It was found that plasma-irradiation can further enhance the functionality and/or add a new surface property of such cellulose derivatives, since one of the characterristics of plasma-irradiation is the fact that it is surface-limited (*ca.* 500—1000 Å).

Hydroxypropylmethylcellulose (HPMC) is one of the most widely used pharmaceutical aids as a binder for tableting, and could have the dual functions as an effect of plasma-irradiation due to the presence of both structural features of HPC and MC. Hydroxypropylmethylcellulose phthalate (HPMCP), used as an enteric coating agent, would have a further functionality in addition to that of HPMC due to the presence of carboxybenzoyl groups. Based on the findings obtained from a series of ESR studies on elucidation of plasma-induced radicals of several cellulose derivatives thus far investigated,[4—7] HPMC and HPMCP are of dual reactive moieties, a plasma-degradable main chain of cellulose and a plasma-crosslinkable side chain structure including a highly plasma-crosslinkable aromatic ring in HPMCP.

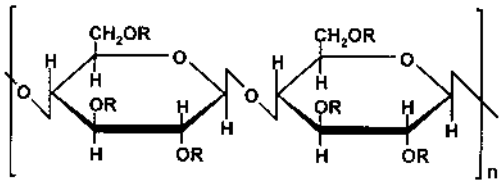
In this paper, we report a further extended work on preparation of a rapid-release tablet being converted into a controlled-release tablet in an experiment using argon plasma-irradiation on double-compressed tablet composed of HPMC or HPMCP as a single wall material.

## Experimental

**Materials** Commercial HPMC (TC-5R) (molecular weight (MW): *ca.* 140000; glass transition temperature ($T_g$): 165 °C, degree of substitution (DS): 1.8—2.0 (methoxyl substitution: 28.0—30.0%, hydroxypropyl substitution: 7.0—12.0%)) and HPMCP (HP-55) (MWv: *ca.* 450000; $T_g$: 145 °C, DS: 1.8—2.0 (methoxyl substitution: 18.0—22.0%, hydroxypropyl substitution: 5.0—9.0%, carboxybenzoyl substitution: 27.0—35.0%)) (Sinetsu Chemicals, Co. Japan) were screened with a 200 mesh sieve and dried *in vacuo* for 24 h. Commercial theophylline was dried *in vacuo* at 60 °C for 24 h and used without further purification.

**Plasma-Irradiation and ESR Spectral Measurement** Powdered samples (50 mg) were placed in a specially designed ampule (30 mm i.d., 100 mm long) with a capillary tube (2 mm i.d.) at the uppermost part. The ampule was filled with argon gas for plasmolysis (0.3 Torr) and sealed. Then the plasma state was sustained for the prescribed period of time by a radio frequency (rf) discharge of inductive coupling using four-loop antenna at 13.56 MHz with the supplied power (50 W). The ESR measurements [JES-RE1X (JEOL) spectrometer with an X-band and 100 KHz field modulation, and a microwave power level of 0.01 mW] were performed while turning the ampule upside down after plasma-irradiation at appropriate intervals. The schematic representation is shown in Fig. 1, which is essentially the same as reported earlier.[9]

**Tablet Preparation** HPMC and HPMCP tablets were obtained by compressing these polymer powder (100 mg) into a flat-faced tablet, 13 mm$\phi$, at a pressure of 200 kg/cm$^2$ for 30 s. The double-compressed tablets were prepared at pressure of 200 kg/cm$^2$ for 30 s from a flat-faced core theophylline tablet (10 mm$\phi$, at a pressure of 40 kg/cm$^2$ for 10 s) and powdered HPMC or HPMCP as a wall material. All flat-faced tablets were prepared using a hand




**Hydroxypropylmethylcellulose (HPMC)**

R= —H , —CH$_3$ or $\left[-CH_2\underset{CH_3}{CH}-O-\right]_m^H$

**Hydroxypropylmethylcellulose phthalate (HPMCP)**

R= —H , —CH$_3$ , $\left[-CH_2\underset{CH_3}{CH}-O-\right]_m^H$ , —COC$_6$H$_4$COOH or $\left[-CH_2\underset{CH_3}{CH}-O-\right]_m$COC$_6$H$_4$COOH

* To whom correspondence should be addressed. e-mail: kuzuya@gifu-pu.ac.jp

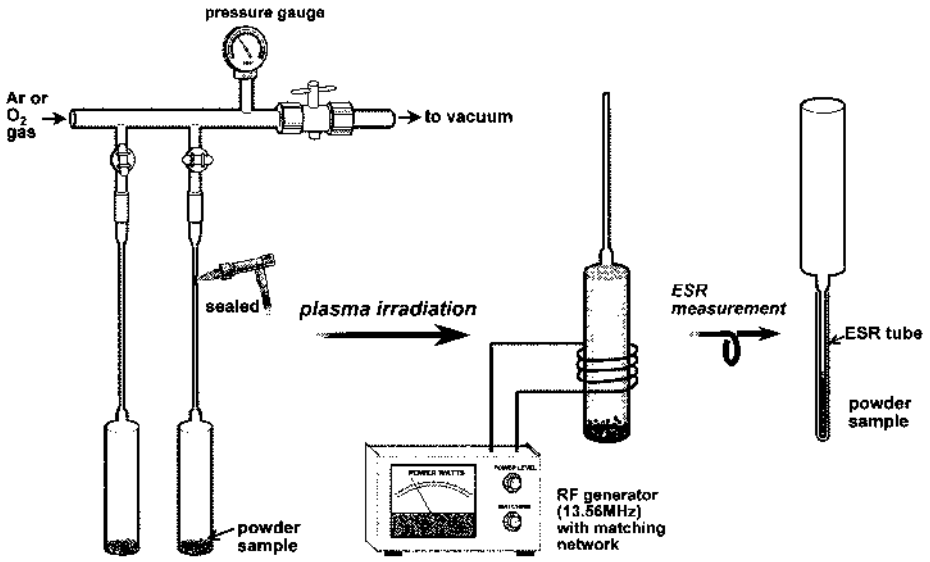



Fig. 1. Schematic Representation of Plasma-Irradiation and ESR Spectral Measurement

press instrument (SSP-10A, Shimadzu Co.) in a tablet die (P/N202-32010, Shimadzu Co.).

**Plasma-Irradiation on Tablet** The apparatus for plasma-irradiation on tablet is essentially the same as used in a previous paper.[3] The plasma state was generated by use of rf discharges of inductive coupling with supplied power of 30—70 W at 13.56 MHz. Flow volume (50 ml/min) and pressure of argon or 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 these polymer tablets induced by plasma-irradiation was determined by measurement of the weight loss at various stages of plasma duration.

**Dissolution Test of Plasma-Irradiated HPMC and HPMCP** The dissolution test of polymer tablets was conduced in distilled water for HPMC and pH=6.8 buffer solution for HPMCP 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 with averages of 5 runs by difference between the tablet weight before and after dissolution.

**Test of Theophylline Release** Test of theophylline release from the double-compressed tablets was conducted according to the standard dissolution method using a rotational basket apparatus (TR-5S3, Toyama Industry) at 37±0.5 °C with 100 rpm in distilled water or in JP XIII 2nd fluid (pH=6.8), as described in the test of tablet dissolution. Released theophylline was periodically assayed by absorption spectrum at the wave-length of 270 nm.

**Scanning Electron Microscope (SEM)** The microscopic changes in the surface morphology of the plasma-irradiated tablet were photographed by SEM (JEOL, JSMT-330A) at an inclination angle of 25 degree with accelerating voltage of 15 kV and magnification of ×500 and ×5000.

## Results and Discussion

**ESR Spectra of Argon Plasma-Irradiated HPMC and HPMCP** With a view of gaining an insight into the nature of argon plasma-induced surface reactions of HPMC and HPMCP, the surface radicals formed were studied by ESR. Figure 2 presents the progressive changes in the room temperature ESR spectra with various plasma duration together with those of EC,[5] hydroxyethylcellulose (HEC),[5] polystyrene (PS)[10] and polyethylenephthalate (PET)[11] for comparisons.

The gross spectral features of HPMC and HPMCP appear to be different from each other, but each spectral pattern remains nearly unchanged in the course of the plasma-irradiation, although the relative intensity of the central peak to the lateral peaks gradually increased in the latter case. It is also

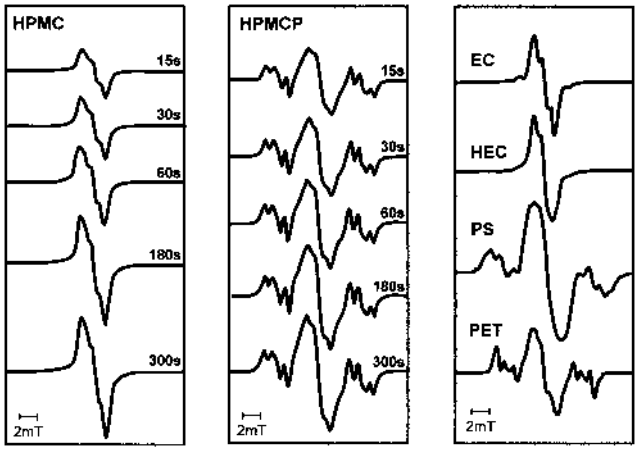



Fig. 2. ESR Spectra of Plasma-Induced Radicals with Various Plasma Duration

seen that the spectral features of HPMC and HPMCP are very similar to those of EC or HEC, and those of PS or PET, respectively.

Note that comparison in the total spectral intensity between HPMC and HPMCP determined by double integration has shown that such an intensity of HPMCP was much higher than that of HPMC by *ca*. 4 times in each measurement.

We have already reported the ESR studies on various cellulose derivatives such as EC, HEC,[5] low-substituted HPC (L-HPC), high-substituted HPC (H-HPC),[6] CMC, Chitin and Chitosan,[7] including several other carbohydrates[9,12,13] with the aids of systematic computer simulations.

Based on a series of such studies, the ESR spectra of plasma-irradiated HPMC can be assumed to consist of dangling-bond sites (DBS) as a major component radical, indicative of the concurrent occurrence of the cross-link reaction in addition to a degradation reaction of cellulose main chain initiated by the 1,4-glucoside bond scission. Likewise, the ESR spectra of plasma-irradiated HPMCP can be assumed to consist mainly of cyclohexadienyl-type radicals formed by a

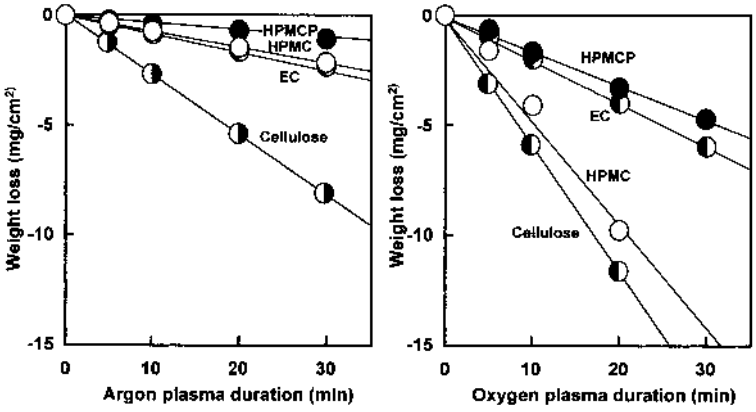



Fig. 3. Effect of Plasma-Irradiation on Polymer Degradation
Plasma conditions: 50 W, 0.5 Torr, Ar or $O_2$ 50 ml/min.

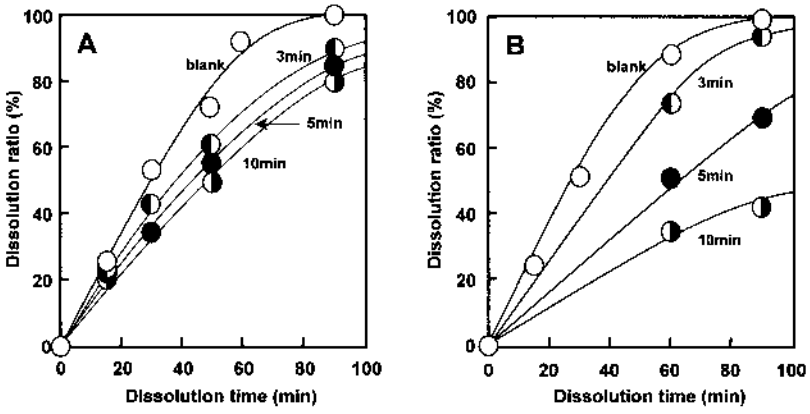



Fig. 4. Effect of Plasma Duration on Dissolution Rate of HPMC in Distilled Water (A) and HPMCP in pH=6.8 Buffer Solution (B)
Plasma conditions: 50 W, 0.5 Torr, Ar 50 ml/min. Polymer tablet: HPMC (100 mg).

random addition of hydrogen to an aromatic ring of the carbobenzoyl group contained as a major substituent (27.0—35.0%), as in the case of PS and PET. Such radicals have a great tendency to undergo the radical recombination, eventually resulting in the formation of DBS[10] which accounts for the progressive increase in intensity of the central peak assignable to DBS in the spectra of HPMCP. It should be noted that these polymers are totally amorphous so that the radical can almost instantly dissipate on exposure to air.[4]

We intend to perform more refined analyses of the component radicals involved in the ESR spectra of HPMC and HPMCP in the future and will be reported elsewhere dealing with only that subject. The present spectral comparisons still provide a good estimate of the surface reactions on such polymers induced by argon plasma-irradiation.

**Degradation Property of HPMC and HPMCP by Plasma-Irradiation** Figure 3 illustrates changes in the weight loss of directly-compressed tablets of HPMC and HPMCP as a function of argon and oxygen plasma-irradiation time, together with those of cellulose and EC for comparisons.

It is seen that each polymer degradation is linearly proportional to the plasma duration, and that oxygen plasma-irradiation accelerates very much the degradation in HPMC and HPMCP relative to that of argon plasma-irradiation due to the occurrence of oxidative decomposition. The degradation rates of HPMC (Ar; $0.07\,mg\cdot cm^{-2}\cdot min^{-1}$, $O_2$; $0.30\,mg\cdot cm^{-2}\cdot min^{-1}$) and HPMCP (Ar; $0.033\,mg\cdot cm^{-2}\cdot min^{-1}$, $O_2$; $0.16\,mg\cdot cm^{-2}\cdot min^{-1}$) are lower than those of cellulose in both argon and oxygen plasma-irradiations.

Comparison in the degradation rates between HPMC and HPMCP has shown that the degradation of HPMCP is much smaller than that of HPMC in both argon and oxygen plasma-irradiations. This can be explained in terms of the fact that a carboxybenzoyl group in HPMCP has a great feasibility of the surface cross-link reaction which is faster in rate than the reaction of plasma-activated oxygen species with the polymer in oxygen plasma-irradiation.

**Changes in Dissolution of HPMC and HPMCP by Argon Plasma-Irradiation** The drug release rate from double-compressed tablet should depend on solubility of the outermost layer. Therefore, we have also measured the changes in the solubility of directly-compressed tablets of HPMC and HPMCP plasma-irradiated for a prescribed period of time.

Figure 4 shows several examples for the effect of argon plasma duration with the output of 50 W on the changes of dissolution rates of HPMC in distilled water (Fig. 4A) and HPMCP in pH=6.8 buffer solution (Fig. 4B).

It is clear that Ar plasma-irradiation onto these tablets caused the decrease in the dissolution rate, as the plasma duration increased in all cases, and a larger suppression of the

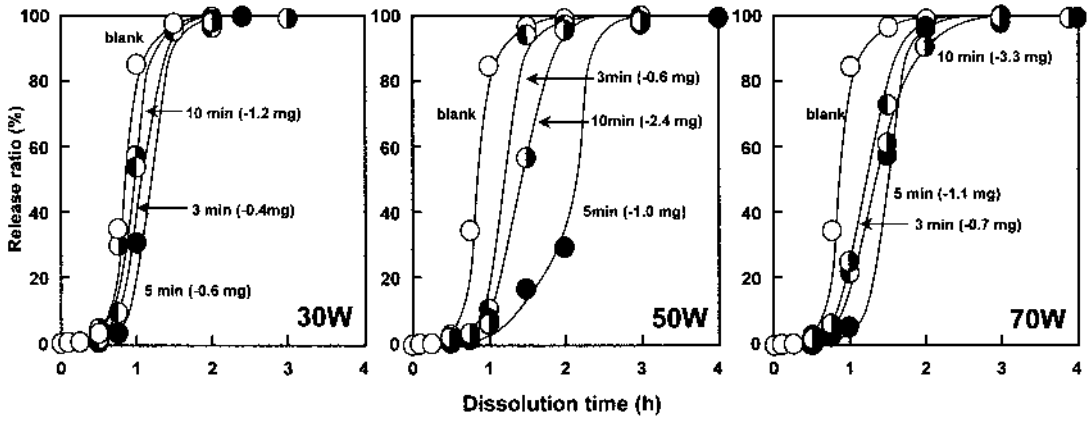



Fig. 5. Effect of Plasma Duration on Release Properties of Theophylline from Plasma-Irradiated Double-Compressed Tablets of HPMC in Distilled Water at Plasma-Supplied Power of 30, 50 and 70 W

Plasma conditions: 0.5 Torr, Ar 50 ml/min. Outer layer: HPMC (100 mg).

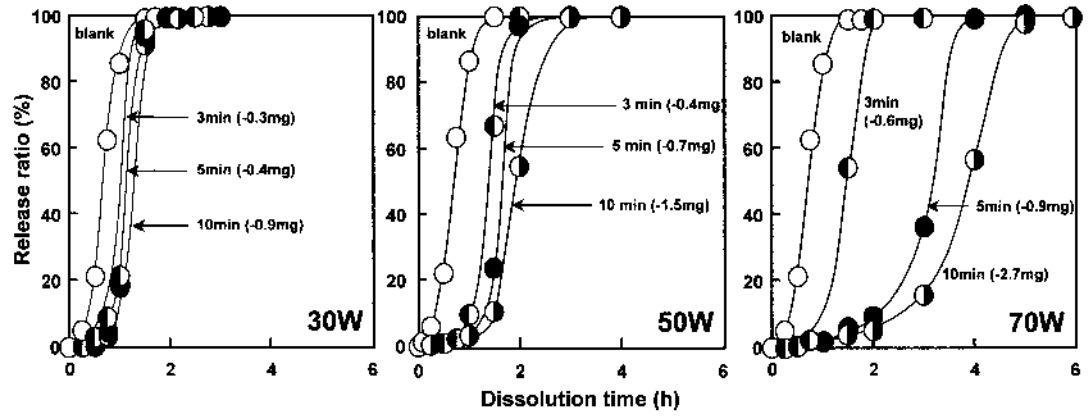



Fig. 6. Effect of Plasma Duration on Release Properties of Theophylline from Plasma-Irradiated Double-Compressed Tablets of HPMCP in pH=6.8 Buffer Solution at Plasma Supplied Power of 30, 50 and 70 W

Plasma conditions: 50 W, 0.5 Torr, Ar 50 ml/min. Outer layer: HPMCP (100 mg).

tablet dissolution can be seen with HPMCP tablet, due to the occurrence of surface cross-link reactions in accordance to the result of degradation properties as shown above.

**Theophylline Release Properties from Plasma-Irradiated Double-Compressed Tablets** Figure 5 shows the dependence of plasma duration with various supplied powers of 30, 50 and 70 W on theophylline release property from double-compressed tablet of HPMC in distilled water.

It is seen that argon plasma-irradiation caused the retardation of theophylline release to an appreciable extent, compared with that of non-plasma irradiated tablet, although it varied somewhat with plasma duration. We have also examined the theophylline release test of the tablets prepared by using a larger amount of HPMC as an outer layer, but it did not improve the release property to such an extent as desired.

Likewise, Fig. 6 shows the effect of plasma duration on theophylline release from the double-compressed tablets of HPMCP in pH=6.8 buffer solution.

It is seen that HPMCP tablet has been changed into sustained-release system with a sigmoid release pattern as plasma supplied power increased, especially at 70 W as a better effect of plasma-irradiation on HPMCP than that on HPMC, although the tablet with 30 W power did not show a sufficient effect on conversion into sustained-release system. The result is closely related to the fact that HPMCP contains a plasma-crosslinkable carboxybenzoyl groups in the side chain.

Based on the fact that the effect of plasma duration on sustained-release pattern varies with plasm-supplied powers, the present tablet of HPMCP is apparently applicable to controlled-release systems having a desired release pattern by selecting the plasma operational conditions.

**SEM Observations of Surface Morphology of Plasma-Irradiated Tablets** In order to understand the factor to control the nature of drug release pattern, the progressive changes in the surface morphology of the plasma-irradiated tablets (×500), and in more microscopic characteristics on the scale of powder particle for tableting (×5000) were monitored by SEM observations. Figure 7 presents several SEM photos on the surface of double-compressed tablets of HPMC and HPMCP, before and after argon plasma-irradiation for 3, 5 and 10 min, respectively.

As can be seen from SEM photos with magnification of ×500 in Fig. 7, the plasma-irradiated HPMC and HPMCP tablets showed the progress of surface softening with the formation of various sizes of micropore, as the plasma duration increased.

In the SEM photo of the tablet surface of HPMC, the unit

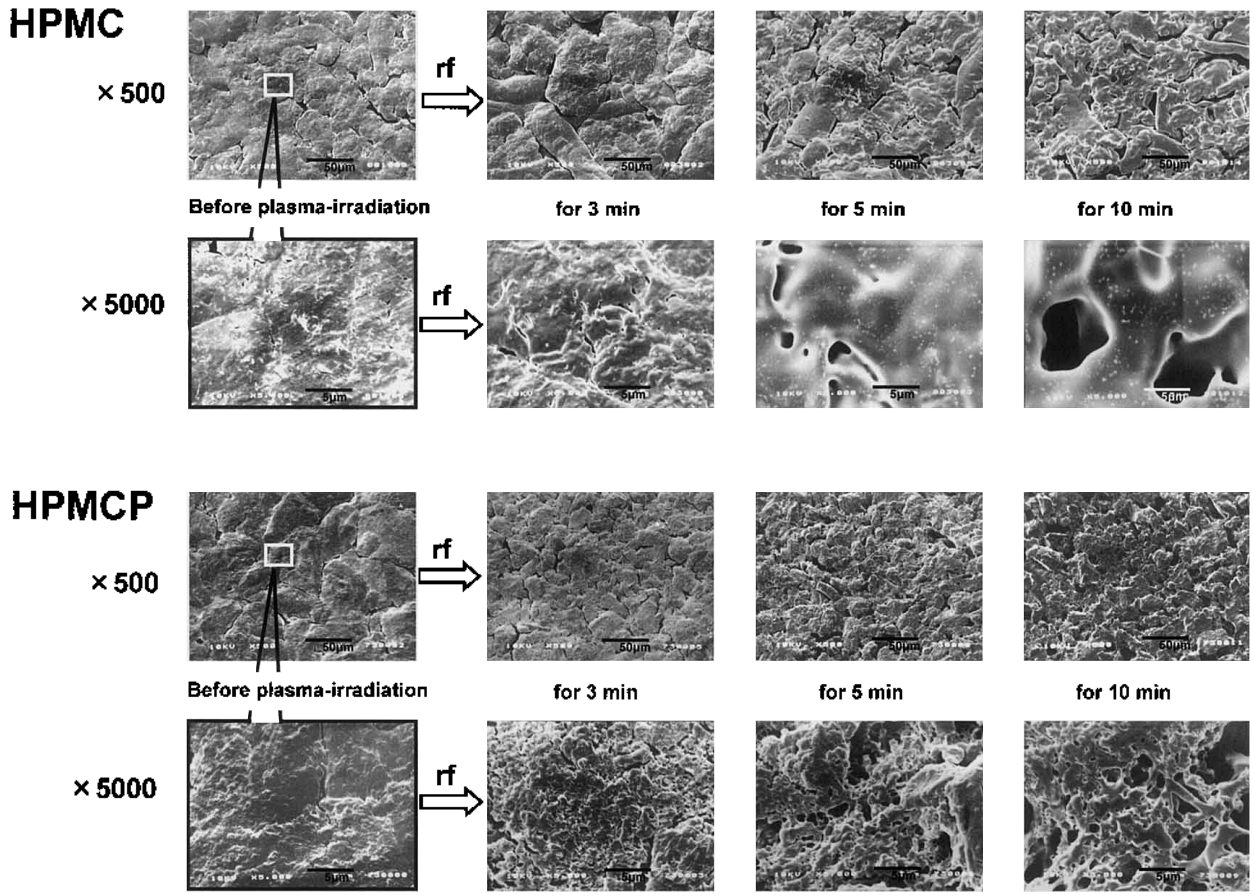



Fig. 7. SEM Photos of Double-Compressed Tablet before and after Argon Plasma-Irradiation for Various Duration
Plasma conditions: 50 W for HPMC and 70 W for HPMCP, Ar 0.5 Torr, 50 ml/min.

shape of powder particle for tableting can still be seen even after 5 min irradiation as in the case before plasma-irradiation, and the space at particle–particle interfaces causes to leach out theophylline, resulting in less effective outer layer of HPMC for retardation of theophylline release, while the HPMCP tablet showed the progress of surface roughening accompanied by clogging the space at particle–particle interfaces, apparently due to a facile cross-link reaction involving carboxybenzoyl groups and degradation reaction of main chain of cellulose.

More microscopic observation with magnification of ×5000 further showed a clear difference in the surface morphological changes between HPMC and HPMCP. Prolongation of plasma-irradiation onto HPMC caused to convert into the smooth film-like surface coupled with a thermal effect of plasma, accompanied by the formation of micropores with an approximate size of 1—3 $\mu$m in diameter. Simultaneously, many convex-shaped swollen parts thought to be a pre-stage of micropore formation can also be seen in the photo of HPMC with plasma duration of 5 min in addition to micropore formed, while the photo of HPMC with plasma duration for 10 min is giving birth to the micropore with a size of more than 10 $\mu$m in diameter, probably due to breaking the swollen parts of softened film-like layer by the physical action of evolved gas scattering. Thus, theophylline can be released more readily through these micropores, which may rationalize the experimental fact that the HPMC tablet with plasma-irradiation for 10 min at 50 W has exhibited more rapid theophylline release than HPMC tablet with plasma-irradiation for 5 min (Fig. 5). Furthermore, the formation of softened film-like surface would concurrently provide one explanation as to why plasma-induced radical observed in HPMC was much lower than that in HPMCP. The radicals once formed in HPMC would readily dissipates due to a rapid segmental motion in softened moieties, thus DBS being observed as a major component radical in the ESR spectrum of HPMC.

On the other hand, it is clearly seen that prolongation of plasma-irradiation onto HPMCP caused to change the tablet surface into a web-like network with surface softening resulting in the generation of micropores with an approximate size of 1—2 $\mu$m.

The cross-link reaction causes the suppression of HPMCP solubility due to increase in its molecular weight, but the tablet surface turned simultaneously to the porous outer layer, so that HPMCP tablet did not convert into delayed-release system, unlike Eudragit L100-55 tablet reported in a previous paper,[3] but the theophylline can be released from HPMCP tablet through the resulting micropores, thereby HPMCP tablet attained a sustained-release system with a sigmoid release pattern. Difference in physicochemical properties between two polymers, Eudragit L100-55 and HPMCP, may be responsible for such a discrepancy in the nature of plasma-driven surface reaction. The crosslinkable part of Eu-

dragit L100-55 with much lower $T_g$ temperature (110 °C) is present in the polymer main chain, resulting in the formation of film-like surface by clogging the space/crack existing at particle–particle interfaces, together with cross-link reactions, while the crosslinkable part of HPMCP is present in the side chain with degradable main chain of cellulose.

Note that the present result also reinforced the mechanism proposed in a previous paper[3] by which Eudragit L100-55 tablet was converted into delayed-release system.

## Conclusion

The present paper has shown that rapid theophylline release from the double-compressed tablet of a water-soluble cellulose derivatives such as HPMC and HPMCP used as a wall material can be suppressed by argon plasma-irradiation and changed into sustained-release system. The result provided a new example that cellulose derivatives widely used as pharmaceutical aids can be also applied to a single outer layer polymer of the double-compressed tablet to fabricate a completely soluble controlled-release system making use of plasma techniques. It was concluded that concurrent occurrence of inter-segmental cross-link reaction and the micropore formation is responsible for conversion of rapid-release system into, not delayed-release system, but sustained-release system.

It is hoped that further devices applicable to a wide range of drugs and polymers will be found in the course of work now in progress to examine the usefulness of plasma techniques for DDS preparations through totally dry process.

**Acknowledgments** This work was financially supported in part by a Grant in Aid of Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (Grant No. 11672147), which is gratefully acknowledged. We are also indebted to Sinetsu Chemicals, Co. Japan for a generous supply of HPMC and HPMCP.

**References**

1) For reviews, see: *a*) Kuzuya M., Matsuno Y., *DDS*, **8**, 149—159 (1993); *b*) Kuzuya M., *Yakugaku Zasshi*, **116**, 266—285 (1996); *c*) *Idem*, *Nihon Byouin Yakuzaishikai Zasshi*, **33**, 84—85 (1997); *d*) Kuzuya M., Kondo S., *Applied Physics*, **69**, 401—405 (2000).
2) Kuzuya M., Kondo S., Sasai Y., *Plasmas and Polymers*, **6**, 147—164 (2001).
3) Kuzuya M., Ito K., Kondo S., Makita Y., *Chem. Pharm. Bull.*, **49**, 1586—1592 (2001).
4) Kuzuya M., Morisaki K., Niwa J., Yamauchi Y., Xu K., *J. Phys. Chem.*, **98**, 11301—11307 (1994).
5) Kuzuya M., Yamauchi Y., Niwa J., Kondo S., Sakai Y., *Chem. Pharm. Bull.*, **43**, 2037—2041 (1995).
6) Kuzuya M., Yamauchi Y., Niwa J., Kondo S., *Proc. Jpn. Symp. Plasma Chem.*, **9**, 55—60 (1996).
7) Kuzuya M., Sasai Y., Kondo S., *J. Photopolym. Sci. Technol.*, **12**, 75—78 (1999).
8) Kuzuya M., Yamauchi Y., Kondo S., *J. Phys. Chem. B.*, **103**, 8051—8059 (1999).
9) Kuzuya M., Noda N., Kondo S., Washino K., Noguchi A., *J. Am. Chem. Soc.*, **114**, 6505—6512 (1992).
10) Kuzuya M., Noguchi A., Ito H., Kondo S., Noda N., *J. Polym. Sci. Polym. Chem.*, **29**, 1—7 (1991).
11) Kuzuya M., Ito H., Sugito M., Kondo S., *J. Photopolym. Sci. Technol.*, **11**, 329—332 (1998).
12) Kuzuya M., Yamauchi Y., *Thin Solid Films*, **316**, 158—164 (1998).
13) Yamauchi Y., Sugito M., Kuzuya M., *Chem. Pharm. Bull.*, **47**, 273—278 (1999).