*Chem. Pharm. Bull.* **44**(6) 1232—1237 (1996) Vol. 44, No. 6

# A New Drug Delivery System Using Plasma-Irradiated Pharmaceutical Aids. VII. Controlled Release of Theophylline from Plasma-Irradiated Polymer-Coated Granules

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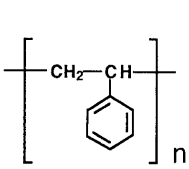
**With a view to expanding the application of a drug delivery system (DDS) preparation using plasma-irradiated pharmaceutical aids for various dosage forms, we studied the theophylline release property from plasma-irradiated polymer-coated granules, the polymers of which differ in the plasma irradiation effect. We used a new type of rotational plasma-irradiation reactor to perform plasma-irradiation uniformly on the surface of polymer-coated granules based on scanning electron microscope (SEM) observation. It was shown that an increase in theophylline release rate with an increase in plasma duration was observed in all polymer-coated granules, although the factors of such release properties vary with the polymers, as evidenced by the SEM observations. Such results provided the criteria for selecting polymer structures for granule coating. Thus, the present method for the control of drug release is considered principally applicable not only to polymer-coated granules but also to various drug forms under consideration of the above criteria.**

**Key words** plasma-processing; polymer-coated granule; theophylline; controlled-release; DDS

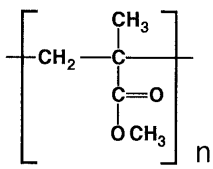
In the past several years, we have reported in detail about plasma-induced free radicals in a number of polymers by ESR spectral measurement and its simulation.[1–12] The results of such study have clarified the molecular mechanism of plasma surface treatment, particularly the effect of plasma irradiation dependent on the polymer structure, thus making it possible to provide a sound basis for future effective experimental design and to develop new applications for the surface processing of the solid materials. As one of the applications in the pharmaceutical field, we have reported on the construction of a new controlled release type drug delivery system (DDS) obtained by oxygen plasma-irradiation on the outermost layer of double-compressed tablets having polymer powder selected on the basis of the plasma irradiation effect.[13–19]

In this report, we studied the control of drug release from a plasma-irradiated polymer-coated granule with an aim to expand the application of this DDS construction method for various dosage forms. We selected four kinds of polymers for coating which differ in the plasma irradiation effect due to differences in polymer structure, namely, polystyrene (PST), typically a plasma-crosslinkable polymer, polymethylmethacrylate (PMMA), a plasma-degradable polymer, polycarbonate (PC), a bifunctional polymer having a plasma-crosslinkable part and a degradable part in the molecular structure, and ethylcellulose (EC), a polymer used widely in the film-coating substrate and microcapsule wall material for pharmaceuticals, and prepared a theophylline granule coated with those polymers.

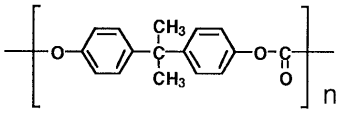
We report in detail the plasma irradiation effect on the theophylline release from these granules.



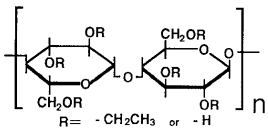
Polystyrene (PST)



Polymethylmethacrylate (PMMA)



Polycarbonate (PC)



Ethylcellulose (EC)

## Experimental

**Materials** Commercial PMMA (degree of polymerization = 7000—7500; Nacalai Tesque), PST (Kishida Chemical) and PC (Aldrich) were each purified according to the usual method, dried *in vacuo* in a desiccator at 60 °C for 12 h and used as a chloroform solution (0.1% (w/v)) for coating. Commercial EC (45—55 cps, 5% toluene + ethanol solution at 25 °C; Tokyo Kasei) was dried *in vacuo* and likewise used as an acetone solution ($8.0 \times 10^{-2}$ % (w/v)) for coating. The molecular weights of the four kinds of polymers obtained were measured by gel permeation chromatography (GPC). The number average molecular weight ($M_n$) and weight average molecular weight ($M_w$) found are shown below. PMMA: ($M_n$) = 580000, ($M_w$) = 1300000 (polydispersity coefficient; $M_w/M_n = 2.35$), PST: ($M_n$) = 160000, ($M_w$) = 330000 ($M_w/M_n = 2.01$), PC: ($M_n$) = 46000, ($M_w$) = 79000 ($M_w/M_n = 1.72$), EC: ($M_n$) = 99000, ($M_w$) = 210000 ($M_w/M_n = 2.10$). Polyvinlypyrrolidone (PVP K90) of $M_w$ = 630000 was purchased from BASF, Japan and used without further purification.

**Preparation of Theophylline Granule** Commercial purified sucrose spheres (purified white sugar 65—85% + corn starch 15—35%) (Freund Industrial Co., Ltd.) 150 g was used as a spherical core substance in preparing a theophylline granule. This core substance, theophylline 35 g and PVP K90 1.7 g as a binding agent was mixed in a granulating machine (CF-Granulator CF-360S, Freund Industrial Co., Ltd.). A mixed solvent of water, ethanol and isopropanol (1 : 2 : 2) containing PVP K90, 25 g was sprayed thereto and 1750 ml of the binding agent was consumed in a centrifugal granulating machine. As a result, a spherical granule retaining a theophylline layer (mean particle size $1.12 \times 10^3$ $\mu$m, deduced from passing particles through various kinds of sieves, theophylline content 15.6%) was prepared on the surface of the sucrose spheres.

**Preparation of Polymer-Coated Granules** Figure 1 shows the outline of a method for polymer coating on a theophylline granule by a conventional evaporator. A flask, of which the inner wall was made

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hydrophobic (nonaqueous) by the method described below, containing a prescribed amount of theophylline granules, was set in the evaporator. A solution of polymer for coating was sprayed on the granules through a glass tube, the tip of which becomes a nozzle, while rotating the flask *in vacuo*. The resulting coated granule was dried *in vacuo* in the desiccator (60 °C, 12 h).

**Introduction of a Hydrophobic Surface onto a Flask for Polymer Coating Use** Diphenyldichlorosilane (0.0118 mol) 3.0 g, triethylamine (0.0247 mol) 2.5 g and methylene chloride 300 ml were added to a 500 ml flask. A dimroth condenser having a calcium chloride tube was attached to the flask, and the solution was heated by reflux for 12 h. After completion of the reaction, the flask was washed thoroughly with methanol.

**Argon Plasma Irradiation on Polymer-Coated Granules** The major problem of plasma irradiation to solid particles such as powder and granules lies in how to devise a method for uniform irradiation. For argon plasma irradiation onto the polymer-coated granules, we contrived a new rotational type plasma reaction apparatus by modifying an evaporator. The outline of this apparatus is shown in Fig. 2. A prescribed amount of the granule sample was placed in a reactor, argon 0.5 torr was sealed in the system, and plasma irradiation was conducted at the output of 30 W by the inductive coupling system using a radio frequency power equipment of 13.56 MHz while rotating the cylinder of the reactor at the rate of 0.5 Hz with an aim to conduct an uniform plasma irradiation on the entire surface of the coated granule.

**Dissolution Test** As for testing drug dissolution from an argon plasma-irradiated polymer coated granule containing theophylline (50 mg), the results were evaluated according to the Rotational Basket Method described in the 12th Vol. of Japanese Pharmacopoeia (Toyama Industry USP (NF) standard dissolution apparatus TR-5S3, eluate: purified water deaerated by boiling, elution test temperature: 37±0.5 °C, revolution speed of basket: 100 rpm). For the amount of theophylline eluted, 4 ml of eluate taken out of the tester at a prescribed time was assayed by UV absorption spectrum at a wavelength of 270 nm.

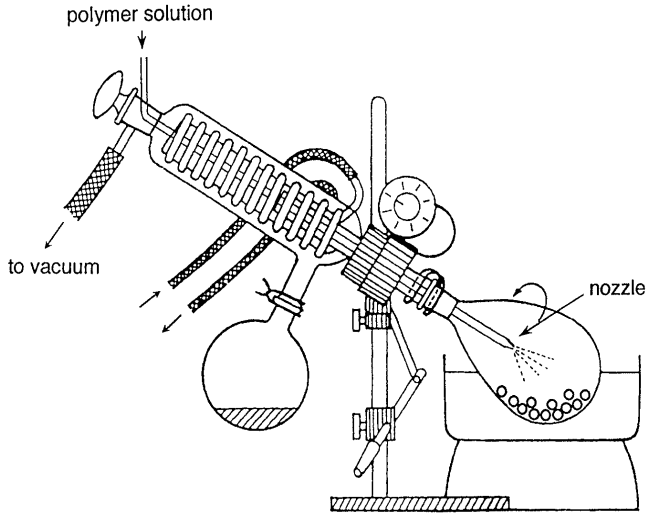


Fig. 1. Schematic Representation of the Preparation of Polymer-Coated Sample

**Scanning Electron Microscope (SEM)** The granule surface was photographed (conditions set: acceleration voltage, 15 kV; multiplying powder, ×500—1000) in order to observe microscopic changes in the surface of various plasma-irradiated polymer-coated granules.

## Results and Discussion

**Ar Plasma Degradation Property of Various Polymers** It is possible that the degradation property of a polymer exposed to plasma irradiation is dependent on the shape of the plasma reactors and samples, and that the rate of the drug release from the coated granules is strongly related to the degradation property of outer layer polymers. Therefore, we studied the degradation property of the outer layer polymer film of polymer-coated granules prepared using a rotational plasma reactor.

Figure 3 illustrates the results of measurement of the weight loss from the polymer degradation. As is clear from Fig. 3, any polymer degrades in proportion to plasma irradiation time, although the degradation of PMMA and PC tends to level off under the present conditions. It can be said that the degradation property of polymers can easily be controlled by the plasma irradiation time. The degradation property is low in the order of PMMA, PC, EC and PST under the same plasma operational conditions.

**Characteristics of Drug Release from Plasma-Irradiated Polymer-Coated Granules** (1) PMMA-Coated Granules: Figure 4 shows the drug dissolution property of a theophylline granule coated with PMMA (film thickness about 25 $\mu$m, 9.8% of the entire granule) under various plasma irradiation conditions.

As is clear from Fig. 4, theophylline release was found even in the non-plasma-irradiated sample, probably because the surface area is large and the film thickness small in a granule compared with a tablet, and a large increase in the drug release rate with plasma irradiation for 30 s was shown. Such an increase in the drug release rate with plasma irradiation may be due to a decrease in the film thickness, arising from PMMA degradation and scattering of the plasma-driven fragment since PMMA is a plasma-degradable polymer. It should be mentioned here that a crosslink-reaction also occurs to a small extent even in plasma-induced degradable PMMA, consistent with a gradual retardation of degradation rate of PMMA (see Fig. 3). Thus, the dissolution rate of theophylline hardly increased with prolongation of the treatment time to a certain extent. Note that a 100% release of theophylline

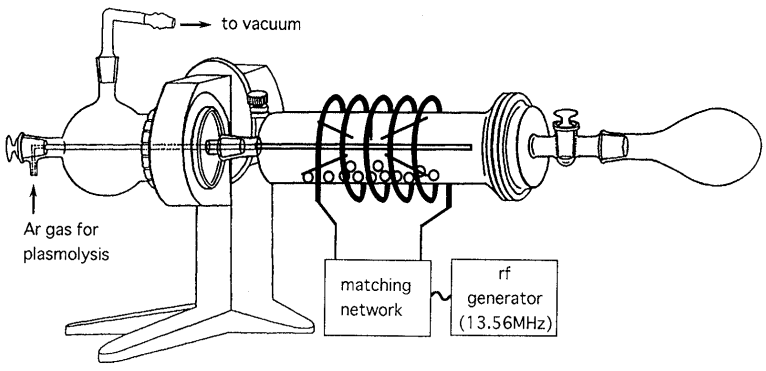


Fig. 2. Schematic Representation of the Preparation of Plasma-Exposed Sample

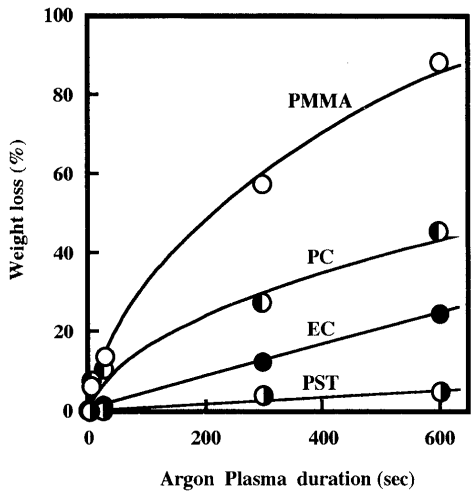


Fig. 3. Effect of Ar Plasma-Duration on Polymer Degradation of Granules-Outer Layer

Plasma conditions: 30 W, 0.5 Torr.

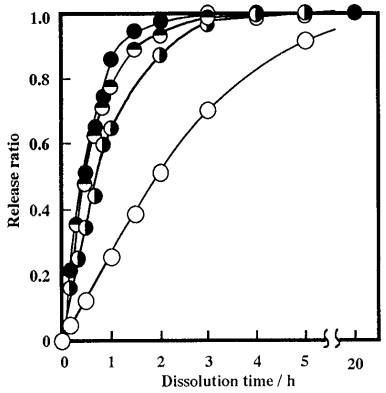


Fig. 4. Effect of Ar Plasma-Duration on the Dissolution Property of Theophylline

Outer layer: polymethylmethacrylate (9.8%). Plasma conditions: 30 W, 0.5 Torr. ○, blank; ◑, 30 s; ◓, 300 s; ●, 600 s.

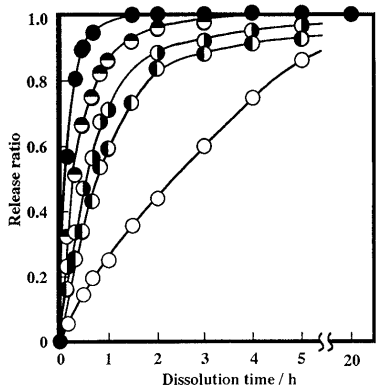


Fig. 5. Effect of Ar Plasma-Duration on the Dissolution Property of Theophylline

Outer layer: polystyrene (9.8%). Plasma conditions: 30 W, 0.5 Torr. ○, blank; ◐, 5 s; ◑, 30 s; ◓, 300 s; ●, 600 s.

was observed eventually in any plasma irradiation time, so that drug degradation due to plasma irradiation is avoided.

(2) PST-Coated Granule: Figure 5 shows the theophylline release property of a granule using PST for coating (film thickness about 25 $\mu$m, 9.8% of the entire granule).

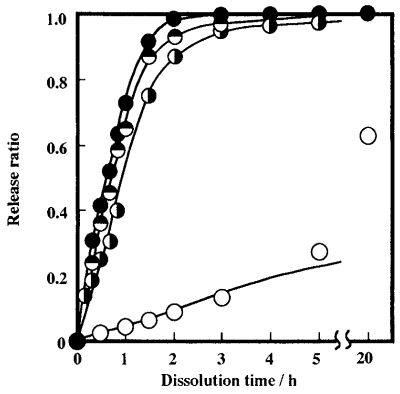


Fig. 6. Effect of Ar Plasma-Duration on the Dissolution Property of Theophylline

Outer layer: polycarbonate (9.8%). Plasma conditions: 30 W, 0.5 Torr. ○, blank; ◑, 30 s; ◓, 300 s; ●, 600 s.

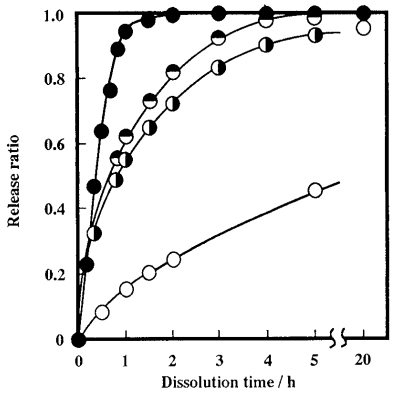


Fig. 7. Effect of Ar Plasma-Duration on the Dissolution Property of Theophylline

Outer layer: ethylcellulose (2.3%). Plasma conditions: 30 W, 0.5 Torr. ○, blank; ◑, 30 s; ◓, 300 s; ●, 600 s.

In the case of PST, a hydrophobic polymer, considerable drug release from the blank itself was also found, as in PMMA. Since PST is a plasma crosslinkable polymer, the release of theophylline from the granule was expected to be suppressed by argon plasma irradiation, but instead the rate of theophylline release was shown to increase with the prolongation of the irradiation time, contrary to expectation.

(3) PC-Coated Granule: Figure 6 shows the effect of plasma irradiation on theophylline release from granules coated with PC (film thickness about 25 $\mu$m). With the PC-coated granule, elution from the blank was considerably low, unlike the case of PMMA and PST. However, a steep rise in drug release occurred with plasma irradiation for 30 s, and the elution rate increased gradually with prolongation of the irradiation time.

In the DDS development of an oxygen plasma-irradiated double-compressed tablet, we have already made it clear that micropores are formed in PC by plasma irradiation.[16] It is possible that this granule irradiated with argon plasma also showed such a theophylline release property because of similar micropores having been formed.

Accordingly, PC film that is converted to a porous film with a crossliking reaction by plasma irradiation is mechanically strong compared with PMMA[16] and can

effectively control the drug dissolution property by plasma irradiation for a short time and at low output. So, this is a polymer suitable for granule coating in this DDS construction.

(4) EC-Coated Granule: Figure 7 illustrates the results of a test on the theophylline release property of the plasma-irradiated EC-coated granule. EC is known to excel in film forming property, to be high in strength and insoluble in water. Where EC was used for coating, the amount of EC coated was 2.3% and the film thickness was *ca.* 6 $\mu$m because of operational difficulties due to the high adhesive properties of EC-coated granules, which is

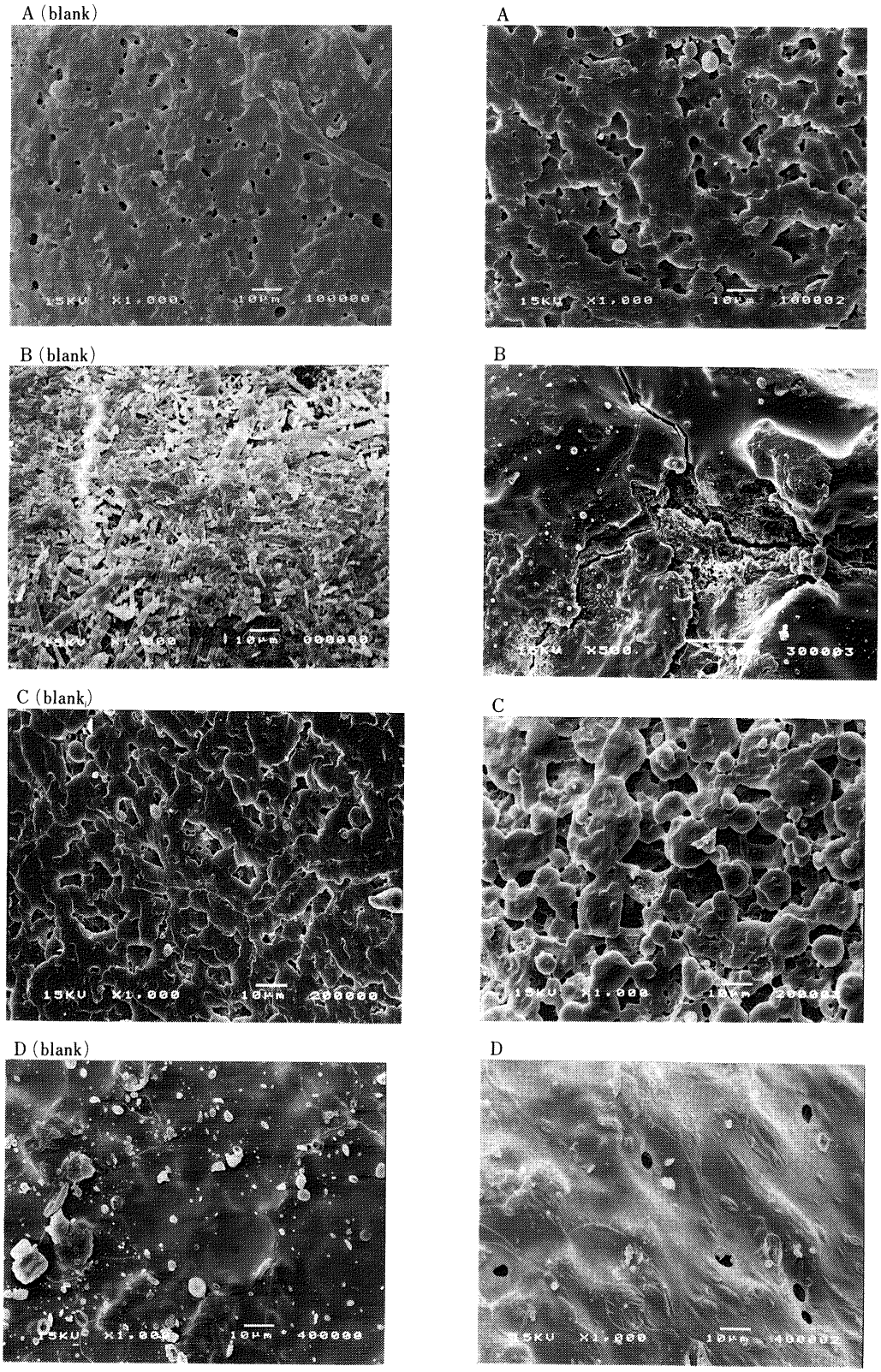


Fig. 8. SEM Photos of the Film Surface of the Various Ar Plasma-Irradiated Polymer-Coated Granules Together with Those of Non-Plasma Irradiated Granules

Outer layer: A, PMMA; B, PST; C, PC; D, EC. Plasma conditions: 30 W, 0.5 Torr.

*ca.* 1/4 the film thickness of the three other coating polymers used, *ca.* 25 $\mu$m. However, the drug release property from the blank was relatively low. On the other hand, the drug release property from the plasma-irradiated EC granule increased markedly, as shown in Fig. 7, and the drug release rate increased with a prolongation of the plasma irradiation time.

Therefore, it is considered possible to prepare a granule in which various release patterns can be controlled effectively by changing the plasma irradiation conditions.

As described above, an increase in the drug release rate was noted with a prolongation of plasma irradiation time, though it varied in degree, in any polymer coated granules. This finding suggests that drug release properties can be controlled by setting the plasma irradiation conditions. However, it has already been made clear that the plasma surface reaction of the polymers used for coating is dependent on chemical structure, and differs from one polymer to another. Nevertheless, similar results were obtained. In order to investigate the cause of these differences, we observed the surface of the plasma-irradiated coated granules by SEM.

**Observations of the Film Surface of Various Plasma-Irradiated Polymer-Coated Granules by SEM Photos** (1) Film Surface of PMMA-Coated Granules: Figure 8A presents one of the SEM photos of the film surface of the plasma-irradiated (300 s) PMMA-coated granule together with that of the non-irradiated granule. As can be seen from this photo, the plasma-irradiated PMMA film showed the progress of surface roughening with a decrease in the film thickness of PMMA due to partial decomposition and scattering compared with the non-irradiated granule. Thus, it is possible that the increase in the drug release rate in the plasma-irradiated granules may be due to a combined factor of the introduction of surface hydrophilicity and/or surface roughening effect and a decrease in the film thickness arising from the degradation and scattering of PMMA.

(2) Film Surface of PST-Coated Granules: Figure 8B shows SEM photos of the plasma-irradiated (300 s) PST-coated granule together with a non-irradiated sample. Formation of film cracks is clearly seen in the plasma-irradiated sample, unlike in the non-irradiated sample, which may have been caused by thermal shrinkage caused by the high degree formation of the cross-linked surface of PST. The drug release property, therefore, must be enhanced by this formation of cracks. So, PST is considered inappropriate as a coating polymer in this kind of drug form which involves the characteristics of plasma irradiation.

(3) Film Surface of PC-Coated Granules: As can be seen from the SEM photos of the PC film surface illustrated in Fig. 8C, the plasma-irradiated PC granule is clearly converted to a porous film. This is due to PC being a bi-functional polymer which has a plasma-crosslinkable part and a degradable part in the main chain, as mentioned earlier. Efficient conversion into a porous film is possible, even by argon plasma irradiation in the PC coated granule, as in the case of the oxygen plasma-irradiated double-compressed tablet already reported.[16] And this conversion can be controlled by changing the conditions for plasma irradiation, which makes it possible to control the drug release rate. So PC is very useful as a polymer for coating, even on granules.

(4) Film Surface of EC-Coated Granules: Figure 8D shows SEM photos of the EC film surface. As is clear from Fig. 8D, EC has a uniform, smooth coated film, but the plasma-irradiated film showed a clear formation of micropores on the surface, although it is completely different from that of PC. On the basis of the results of ESR analysis of plasma-irradiated EC, we have already clarified that EC has a strong cross-linking property compared with non-substituted cellulose.[10,11] The softening point of EC is also relatively low (140 °C). When such physicochemical properties of EC are considered, the micropores of EC formed are presumably produced not by the effect of plasma-irradiation dependent on the chemical structure, but by physical actions such as evolved gas scattering accompanied by softening of the EC film due to a thermal effect in the course of plasma irradiation. In fact, a simple heat treatment applied to the EC-coated granule demonstrated a similar formation of micropores to that confirmed by SEM observation. Thus, as a polymer for the coating of granules which makes use of the characteristics of plasma-irradiation, EC is considered inappropriate, as is PST.

## Conclusion

In particle drug preparations represented by powders, granules and microcapsules, an efficient polymer coating of uniform film thickness onto the surface of these dosage forms is an important issue for the controlled release DDS preparations.

In the present study, we have contrived a new type of rotational plasma irradiation reactor which has made it possible to perform plasma irradiation uniformly on the surface of a polymer in granules based on the SEM observation. Plasma irradiation on various polymer-coated granules each having a different plasma reaction property was conducted. And a similar drug release property, *i.e.* an increase in the theophylline release rate, though varied in degree, with an increase in the plasma irradiation time, was obtained in all the polymer-coated granules tested.

SEM observations on the surface condition of various plasma-irradiated, coated granules showed that the factors of such drug dissolution properties are subject to the influence not only of the polymer reaction property as a plasma-irradiation effect but also the physicochemical properties derived from the polymer structure itself.

Such results are useful for selecting polymers for coating for future experimental designs. The principle of this method using a rotational plasma reactor is considered applicable not only to polymer-coated granules but also to various dosage forms, including multi-layered particles.

**Acknowledgment** This work was financially supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (Grant No. 06672148), which is gratefully acknowledged.

**References**


1) Kuzuya M., Noguchi A., Ishikawa M., Koide A., Sawada K., Ito A., Noda N., *J. Phys. Chem.*, **95**, 2398 (1991).
2) Kuzuya M., Noguchi A., Ito H., Kondo S., Noda N., *J. Polym. Sci. Polym., Chem.*, **29**, 1 (1991).
3) Kuzuya M., Ito H., Kondo S., Noda N., Noguchi A., *Macromolecules*, **24**, 6612 (1991).
4) Kuzuya M., Noda N., Kondo S., Washino K., Noguchi A., *J. Am. Chem. Soc.*, **114**, 6505 (1992).
5) Kuzuya M., Kondo S., Ito H., Noguchi A., *Appl. Surf. Sci.*, **60/61**, 416 (1992).
6) Kuzuya M., Ishikawa M., Noguchi A., Sawada K., Kondo S., *J. Polym. Sci. Polym., Chem.*, **30**, 379 (1992).
7) Kuzuya M., Sawada K., Takai T., Noguchi A., *Polymer J.*, **25**, 75 (1993).
8) Kuzuya M., Niwa J., Ito H., *Macromolecules*, **26**, 1990 (1993).
9) Kuzuya M., Niwa J., Yamauchi Y., Kondo S., *J. Photopolym. Sci. Technol.*, **7**, 315 (1994).
10) Kuzuya M., Morisaki K., Niwa J., Yamauchi Y., Xu K., *J. Phys. Chem.*, **98**, 11301 (1994).
11) Kuzuya M., Yamauchi Y., Niwa J., Kondo S., Sakai Y., *Chem. Pharm. Bull.*, **43**, 2037 (1995).
12) Kuzuya M., Niwa J., Noguchi T., *Polymer J.*, **27**, 251 (1995).
13) Kuzuya M., Noguchi A., Ito H., Ishikawa M., *DDS*, **6**, 119 (1991).
14) Kuzuya M., Ito H., Noda N., Yamakawa I., Watanabe S., *DDS*, **6**, 437 (1991).
15) Yamakawa I., Watanabe S., Matsuno Y., Kuzuya M., *Biol. Pharm. Bull.*, **16**, 182 (1993).
16) Ishikawa M., Matsuno Y., Noguchi A., Kuzuya M., *Chem. Pharm. Bull.*, **41**, 1626 (1993).
17) Ishikawa M., Noguchi T., Niwa J., Kuzuya M., *Chem. Pharm. Bull.*, **43**, 2215 (1995).
18) Kuzuya M., Ishikawa M., Noguchi T., Niwa J., Kondo S., *Chem. Pharm. Bull.*, **44**, 192 (1996).
19) For reviews, see; Kuzuya M., Matsuno Y., *DDS*, **8**, 149 (1993); Kuzuya M., *Farumashia*, **30**, 511 (1994).