A New Drug Delivery System Using Plasma-Irradiated Pharmaceutical Aids. VIII. Delayed-Release of Theophylline from Double-Compressed Tablet Composed of Eudragit as Wall Material

Masayuki KUZUYA,*[,a] Kousuke ITO,[a] Shin-ichi KONDO,[a] and Yoshimitsu MAKITA[b]

Laboratory of Pharmaceutical Physical Chemistry, Gifu Pharmaceutical University,[a] 5–6–1 Mitahora-Higashi, Gifu 502–8585, Japan and Pharmaceutical & Technology Laboratory, Sanwa Kagaku Kenkyusho Co. Ltd.,[b] 855–1 Mitahora, Gifu 502–0004, Japan. Received July 31, 2001; accepted September 14, 2001

The rapid release from a double-compressed tablet containing theophylline as a core drug with the pH-dependent water-soluble polymers, Eudragit L100, S100 or L100-55 used as a wall material was suppressed by argon plasma-irradiation due to an effect of inter-segmental cross-link reactions on the decrease in the surface polymer solubility of outer layer. In addition, the rapid theophylline release from the double-compressed tablet of Eudragit L100-55 with a lower glass transition temperature (T_g) has converted into the delayed-release system under a set of plasma operational conditions due to an additional effect of plasma heat flux on softening of Eudragit L100-55 surface resulting in the formation of the film-like surface with a particle–particle interlinking of the outer layer.

Key words plasma technique; double-compressed tablet; lag time; Eudragit; delayed-release; time-controlled delivery system

In previous papers in this series on preparation of multilayered particles for use in a drug delivery system (DDS) with plasma techniques, we have reported that novel controlled-release tablets can be obtained by oxygen plasma-[1—6] or argon plasma-irradiation[7—9] on the outermost layer of double-compressed tablets.[10] These latter tablets are theophylline as a core material and water-soluble polymers, polymethacrylic acid (PMAA) or polyacrylamide (PAAm) as a single wall material. The drug release has been controlled by occurrence of the surface cross-link reaction by argon plasma-irradiation leading to suppression of the tablet surface solubility, since one of the characteristic of plasma treatment is the fact that it is surface-limited.[8]

For the most suitable therapy, a wide variety of approaches of controlled-release delivery system have been thus far investigated for oral application. Of these approaches, preparations of delayed-release systems have been noted as orally applicable delivery systems which are useful for the time-controlled delivery of a drug in the gastrointestinal tract.[11—14] Time-controlled release system has a function of timer, so that a main technical point for the development of this system is how to control a lag time and to control a drug release after lag time.

It is well known that copolymers of methacrylic and acrylic monomers including their derivatives with the various combinations and composition ratios are used as pharmaceutical aids for enteric coating agents commercially known as "Eudragit." These Eudragit polymers turn to be water-soluble in a certain specific pH solution, and they show a different dissolution rate.

We previously reported that a considerable amount of dangling bonds were produced on powder of water-soluble PMAA by argon plasma-irradiation, and suggested that the cross-link reaction occurred partially in PMAA, although it is classified as a plasma-degradable polymer.[15] On the other hand, acrylic polymers such as PAAm and polyethylacrylate (PEA) are well known to be one of the typical plasma crosslinkable polymers.

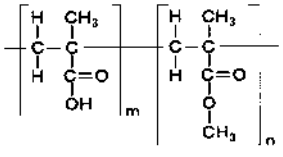
Since methacrylic and acrylic monomers are one of the component polymers in Eudragits, argon plasma-irradiation would lead to the suppression of Eudragit solubility even in higher than dissociable pH-value solution for a certain period of time. Thus, when an Eudragit polymer is used as the wall material of the double-compressed tablet, the drug release rate from the tablet can be controlled and/or retarded by argon plasma-irradiation.

With this expectation in mind, the present work has been undertaken to examine the possibility 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 theophylline as a core material and Eudragit polymers such as Eudragit L100, L100-55 and S100 as a single wall material.

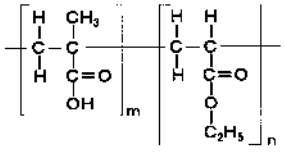
Experimental

Materials Each of commercial Eudragits (Rohm Pharma (Germany), distributed by Higuchi Shoukai Co. (Japan)) were purified by dissolving it (4 g) in methanol (100 ml) and precipitating in water (2 l). Then, it was pulverized and screened through prescribed mesh sieves. Powdered materials thus obtained were dried *in vacuo* for 24 h before use. The average molecular weight (M.W.) and glass transition temperature (T_g) was *ca.* 250000 and >160 °C for L100, *ca.* 250000 and 160 °C for S100, and *ca.* 150000 and 110 °C for L100-55, respectively. The dissociable pH value of each Eudragit is pH=6.0 for L100, pH=7.0 for S100 and pH=5.5 for L100-55. Commercial theophylline (Nacalai Tesque Inc.) was dried *in vacuo* at 60 °C for 24 h, and used without further purification.

Tablet Preparation Each of Eudragit tablets, for the test of plasma-induced degradation and change in solubility at various aqueous pH solution, was obtained by compressing Eudragit powder (100 mg of the fractions screened through a 200-mesh pass sieve) into a flat-faced tablet (13 mmϕ) 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 (50 mg, 10 mmϕ) was first prepared at a pressure of 40 kg/cm^2 for 10 s, and then the core tablet was



Eudragit L100 (m:n=4:6 , soluble at pH>6.0)
Eudragit S100 (m:n=3:7 , soluble at pH>7.0)



Eudragit L100-55 (m:n=4:6 , soluble at pH>5.5)

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

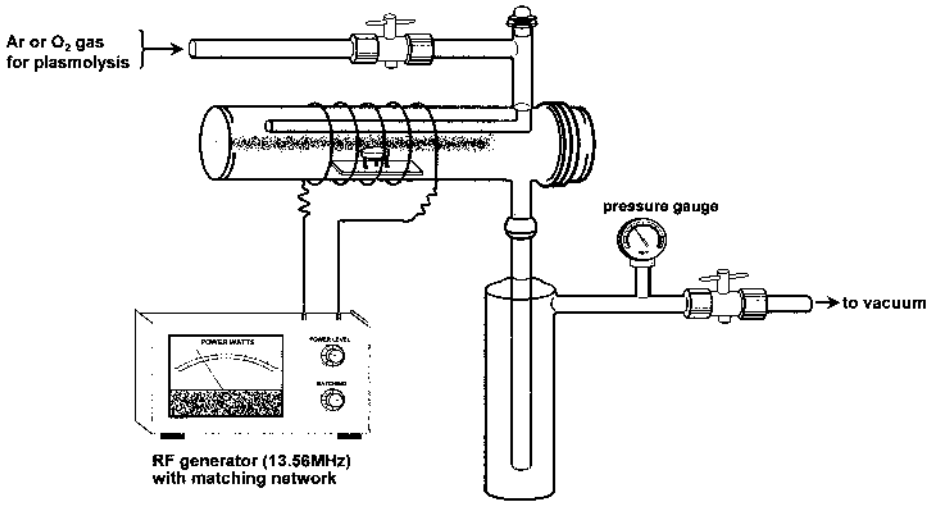


Fig. 1. Experimental Set-up for Plasma-Irradiation on Double-Compressed Tablets

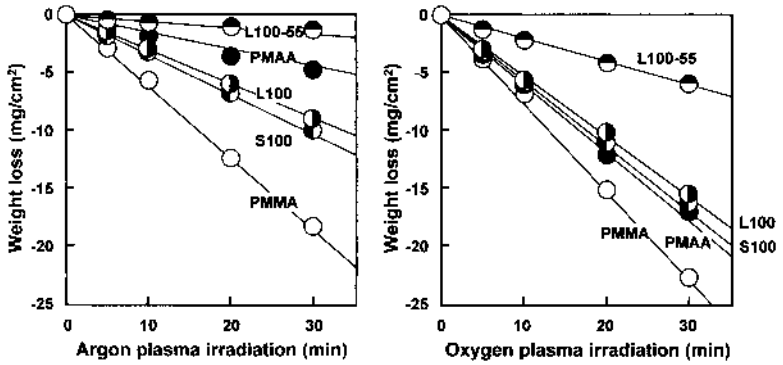


Fig. 2. Effect of Plasma-Irradiation on Eudragit Degradation
Plasma conditions: 50 W, 0.5 Torr, Ar or O_2 50 ml/min.

placed onto half of the prescribed amount of powdered Eudragit (50 mg) as a wall material in a tablet die. After the rest of the powdered polymer (50 mg) 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/N202-32010, Shimadzu Co.).

Plasma-Irradiation A schematic representation of the apparatus for plasma-irradiation is shown in Fig. 1, and this apparatus is essentially the same as reported earlier.[1)] The plasma state was generated by use of radio frequency discharges of inductive coupling with four loop antenna at 13.56 MHz with supplied power of 10—50 W. 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 (230 mm long, 45 mmϕ) to ensure homogeneous exposure to plasma gas.

Degradation rate of Eudragit tablets induced by plasma-irradiation was carried out according to the method similar to the above, and determined by measurement of the weight loss at various stages of plasma duration.

The temperature change in the tablet surface during the course of plasma-irradiation was measured by placing a temperature indicator tip measurable for 50—200 °C (4 mmϕ), comercially known as "Thermo Label 5E" (Nichiyugiken Kogyo Co., Ltd.) on the tablet under a prescribed operational conditions using the same apparatus as above.

Dissolution Test of Plasma-Irradiated Eudragit Tablet The dissolution test of polymer tablets was conducted in a phosphate buffer solution of pH=6.5 for Eudragit L100 and L100-55, and pH=7.0 for Eudragit S100 according to 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 of plasma-irradiated tablet before and after dissolution. The tablet weight after dissolution for a prescribed period of time was measured after drying *in vacuo*.

Test of Theophylline Release Test of theophylline release from the double-compressed tablets was conducted in a phosphate buffer solution of pH=6.5±0.05, 7.0±0.05, 7.5±0.05 or 8.0±0.05, respectively, by the method described above. Released theophylline was periodically assayed by absorption spectrum (UV-3100DS, Shimadzu Co.) at the wave-length of 270 nm.

Scanning Electron Microscope (SEM) The microscopic changes in the surface of the plasma-irradiated tablet were photographed by SEM (JEOL, JSMT-330A) with accelerating voltage of 15 kV and magnification of ×750 and ×2000.

Heat Treatment without Plasma-Irradiation The double-compressed tablet was heated at 130 °C using an external flexible heater (FHU-6, Tokyo Garasu Kikai Co., Ltd.) winded onto the reaction chamber used for plasma-irradiation under an atmospheric pressure of argon for a prescribed period of time, and then submitted to the test of theophylline release as above.

Results and Discussion

Degradation Property of Eudragits by Plasma-Irradiation In order to understand the nature of plasma-irradiation effect on degradation of Eudragits, we first carried out argon plasma- and oxygen plasma-irradiation on several directly-compressed tablets of Eudragit polymers. The result is shown in Fig. 2, together with those of PMAA and polymethylmethacrylate (PMMA) for comparisons.

It is seen that each polymer degradation is linearly proportional to the plasma duration, and degradation rates of three Eudragit polymers, L100 (Ar; 0.30 mg·cm^{-2}·min^{-1}, O_2; 0.53 mg·cm^{-2}·min^{-1}), S100 (Ar; 0.33 mg·cm^{-2}·min^{-1}, O_2;

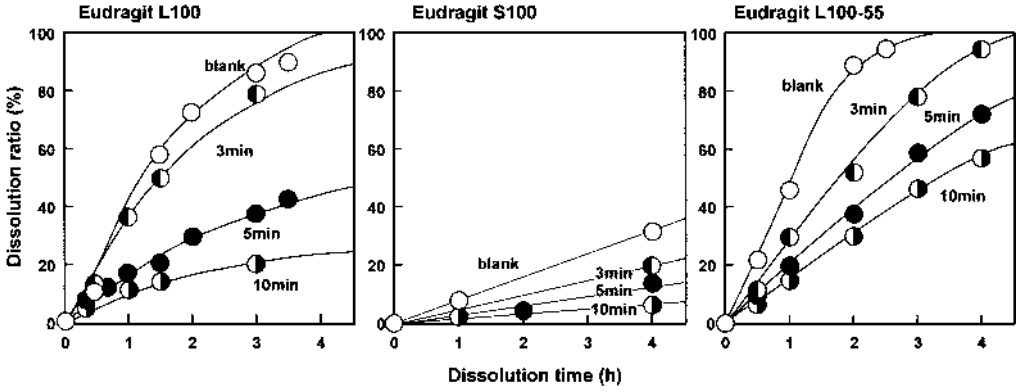


Fig. 3. Effect of Plasma Duration on Dissolution Rate of Eudragit Tablets

L100 tablet in pH 6.5 solution, S100 tablet in pH 7.0 solution, L100-55 tablet in pH 6.5 solution.

$0.57\,mg\cdot cm^{-2}\cdot min^{-1}$) and L100-55 (Ar; $0.033\,mg\cdot cm^{-2}\cdot min^{-1}$, O_2; $0.22\,mg\cdot cm^{-2}\cdot min^{-1}$) are all lower than that of typical plasma-degradable PMMA in both oxygen and argon plasma-irradiation.

Comparison in the degradation rates between oxygen and argon plasma-irradiation has clearly shown that the effect of argon plasma-irradiation is much smaller than that of oxygen plasma-irradiation. This indicates that polymers are generally more prone to undergo the surface cross-link reactions with argon plasma-irradiation than with oxygen plasma-irradiation due to the absence of oxidative decomposition.[10)]

In addition, the rate of degradation of L100-55 was the least with either oxygen or argon plasma-irradiation. The result clearly stems from the fact that Eudragit L100-55 contains a typical plasma-crosslinkable PEA part, unlike Eudragit L100 and S100.

Changes in Water-Solubility of Eudragits by 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 pH-dependent solubility of the compressed tablets of Eudragit L100, S100 and L100-55 plasma-irradiated for a prescribed period of time.

Figure 3 shows several examples for the effect of Ar plasma-irradiation on the changes of dissolution rates of Eudragit tablets in pH=6.5 solution for L100 and L100-55, and pH=7.0 for S100.

It is clear that Ar plasma-irradiation onto the Eudragit tablets caused the decrease in the dissolution rate, as the plasma duration increased in all cases, and a larger effect can be seen with L100-55 tablet. The result clearly stems from the occurrence of surface cross-link reactions induced by Ar plasma-irradiation.

Effect of Ar Plasma-Irradiation on Release Properties of Theophylline from Double-Compressed Tablets We have examined the effect of plasma-irradiation on release properties of theophylline as a model drug from the double-compressed tablets under various plasma operational conditions. Figure 4 shows the effect of plasma duration on theophylline release properties in pH 6.5 buffer solution from Ar plasma-irradiated double-compressed tablets using L100 as an outer layer.

It is seen that plasma-irradiation caused the retardation of theophylline release to an appreciable extent, compared with

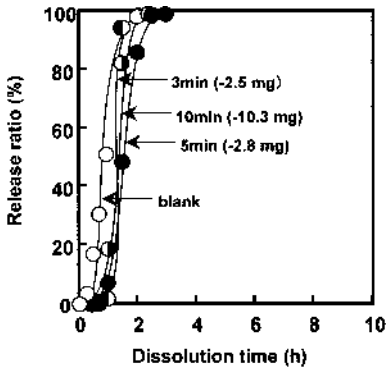


Fig. 4. Effect of Plasma Duration on Theophylline Release Properties in pH 6.5 Buffer Solution from Plasma-Irradiated Double-Compressed Tablets Using Eudragit L100 as Outer Layer

Values shown in parentheses present the weight loss of the tablet after plasma-irradiation. Plasma conditions: 50 W, Ar 0.5 Torr, 50 ml/min.

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 L100 as an outer layer, but it did not improve the release pattern to such an extent as desired.

Likewise, Fig. 5 shows the theophylline release profiles from the plasma-irradiated double-compressed tablets of Eudragit S100 in pH 7.0, 7.5 and 8.0 buffer solution. It is seen that theophylline release started after *ca.* 1—2 h of lag time in all pH solutions even from the controlled tablet (non-plasma-irradiated) due to a low dissolution rate of Eudragit S100 that contains more non-soluble PMMA moiety than Eudragit L100 does. And, all the tablets plasma-irradiated for 3, 5 and 10 min have clearly shown to convert into a sustained-release tablet with a sigmoid release pattern and it takes as long as 20 h for the theophylline release to complete in pH 7.0 and 7.5 buffer solutions. It was also shown that the retardation of theophylline release decreased as pH value increased, apparently due to a higher dissolution rate of Eudragit S100 in higher pH solution.

Figure 6 shows the effect of plasma duration on theophylline release profiles in pH 6.5 buffer solution from the double-compressed tablets of Eudragit L100-55 plasma-irradiated with various supplied powers, 50, 30 and 10 W. It is seen that the effect of plasma duration on theophylline release pattern varies with plasma-supplied powers to a consid-

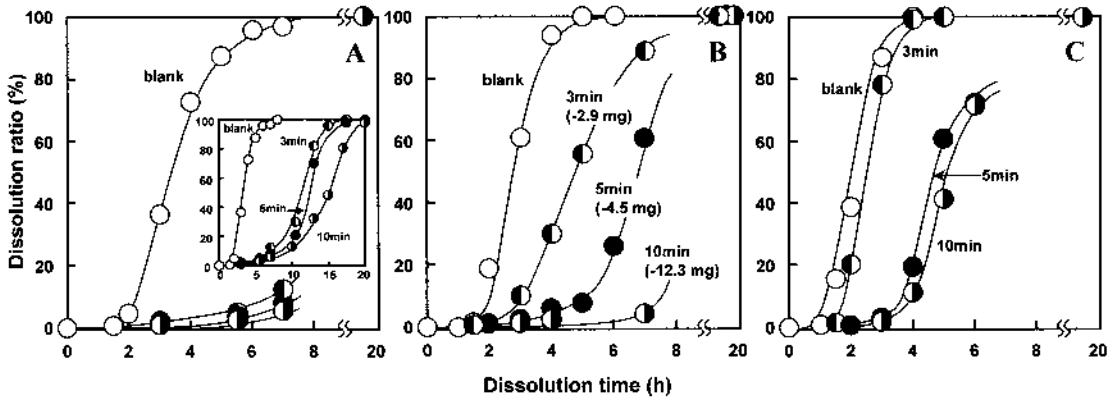


Fig. 5. Effect of Plasma Durations on Theophylline Release Properties in Various Buffer Solution from Plasma-Irradiated Double-Compressed Tablets Using Eudragit S100 as Outer Layer

A: pH 7.0, B: pH 7.5, C: pH 8.0. Values shown in parentheses present the weight loss of the tablet after plasma-irradiation. Plasma conditions: 50 W, Ar 0.5 Torr, 50 ml/min.

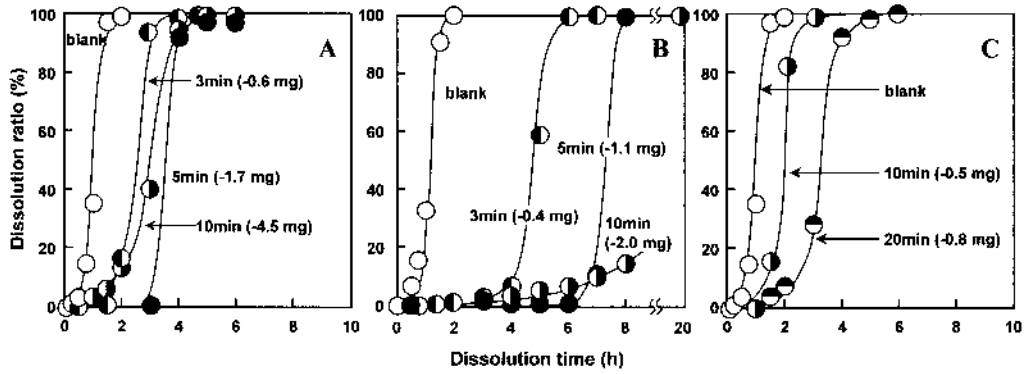


Fig. 6. Effect of Plasma Durations on Theophylline Release Properties in pH 6.5 Buffer Solution from Plasma-Irradiated Double-Compressed Tablet Using Eudragit L100-55 as Outer Layer with Various Output of Plasma Powers

A: 50W, B: 30W, C: 10W. Values shown in parentheses present the weight loss of the tablet after plasma-irradiation. Plasma conditions: Ar 0.5 Torr, 50 ml/min.

erable extent. Clearly, Eudragit L100-55 tablets plasma-irradiated for 3 and 5 min with 50 and 30 W powers have produced a considerable prolongation of lag-time, especially for the tablet with 5 min irradiation at 30 W, and then have rapidly released the theophylline thereafter, being converted into the delayed-release tablet, although the tablet plasma-irradiated for 10 min did not show such a release pattern, which exhibited a very slow theophylline release with a different pattern. (*vide infra*) The result is closely related to the fact that Eudragit L100-55 contains a plasma-crosslinkable PEA part in the main chain.

The tablet with 10 W power, however, did not show such an effect even with 20 min of plasma duration, indicating that the plasma power of 10W is too weak to convert the tablet into delayed-release system.

This is the first example for preparation of the delayed-release tablets by making use of plasma techniques , which is apparently applicable for time-controlled release systems having a desired lag-time by selecting the plasma operational conditions.

SEM Observations of Surface Characteristics of Plasma-Irradiated Tablets With a view of gaining an insight into the factor to controls the nature of drug release pattern, the changes in the surface characteristics of the plasma-irradiated tablets were monitored by SEM observations with an inclination angle of 25 degree. Figure 7 presents several SEM photos of the surface of double-compressed tablets composed of Eudragit L100 and S100 used for an outer layer, respectively, before and after argon plasma-irradiation for 3, 5 and 10 min with conceptional illustration for preparation of double-compressed tablet and plasma-irradiation.

As can be seen from Fig. 7, the plasma-irradiated Eudragit L100 and S100 tablets showed the progress of surface roughening with the formation of micropore similar to each other, as the plasma duration increased. However, the effect of plasma duration on the micropore formation is different from each other. Eudragit S100 tablet produced more micropores accompanied by more surface softening than Eudragit L100 did. This is clearly derived from the presence of PMMA moiety with a higher ratio in the copolymer main chain of Eudragit S100 than that in Eudragit L100. PMMA is well known as one of the plasma-induced degradable polymers and of lower T_g temperature (T_g: 105 °C for PMMA and 228 °C for PMAA), leading to more the decomposition and scattering in this moiety of Eudragit S100.

Likewise, Fig. 8 shows the SEM photos with effect of plasma duration on the progressive changes in the surface morphologies for the case of Eudragit L100-55 tablets at the plasma powers of 50, 30 and 10 W. As is clear from Fig. 8, the SEM pictures of Eudragit L100-55 tablet are largely different in the surface morphology from those shown in Eudragit L100 and S100. The progress of more softened-sur-

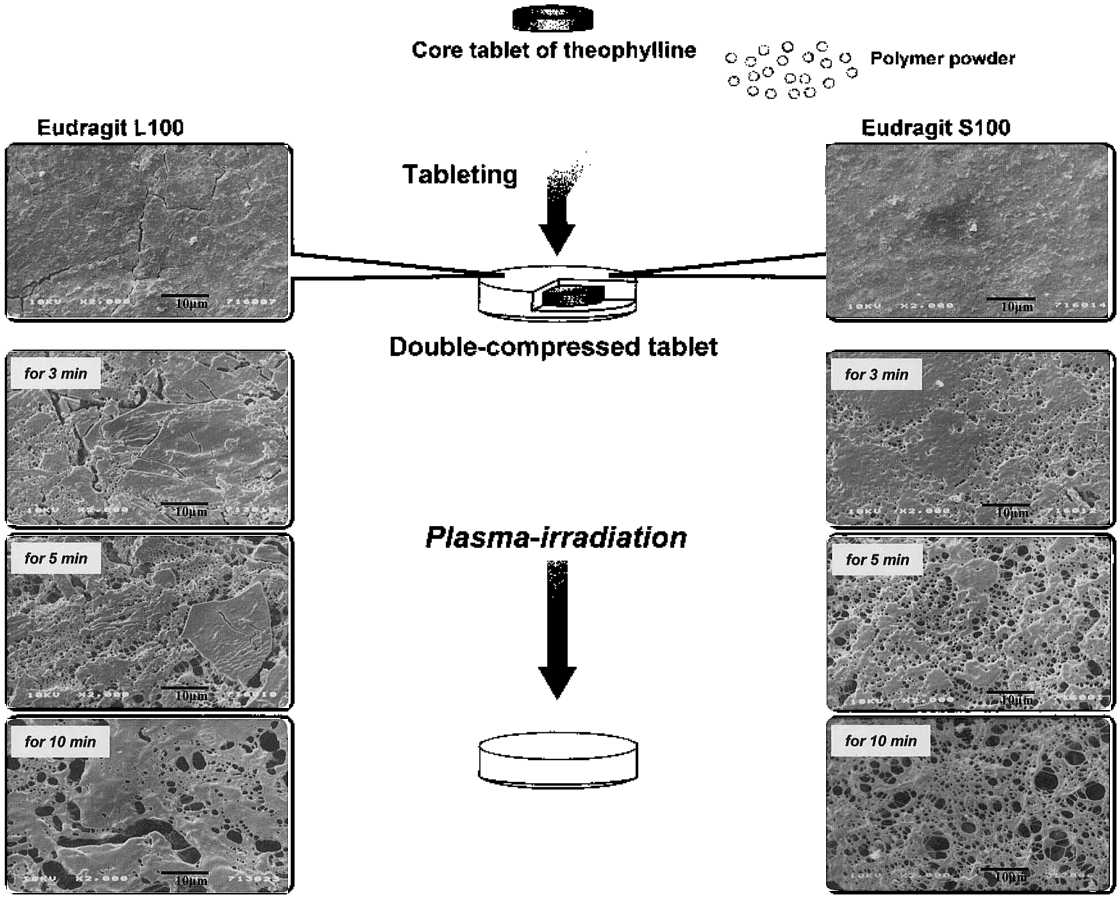


Fig. 7. SEM Photos of Double-Compressed Tablet before and after Argon Plasma-Irradiation for Various Duration
Plasma conditions: 50 W, Ar 0.5 Torr, 50 ml/min. SEM magnification: ×2000.

face can be seen, especially the one for more than 5 min irradiation at the powers of 50 and 30 W, resulting in the formation of film-like surface by clogging the crack existing at particle-particle interfaces in place of micropore formation. This is apparently derived from relatively low T_g temperature of Eudragit L100-55 (See, Experimental section), containing crosslinkable PEA part in the polymer main chain of Eudragit L100-55.

However, it has been shown that the tablet surface with plasma-irradiation for 10 min at the powers of 50 and 30W has converted into the porous outer layer, not by the effect of plasma-irradiation, but by physical actions such as evolved gas scattering accompanied by softening of the Eudragit L100-55 due to the plasma heat flux in the course of plasma-irradiation. Thus, the formation of porous outer layer in Eudragit L100-55 should be considered distinct in nature from the micropore formation in Eudragit L100 and S100.

Mechanistic Implications for Conversion of Rapid-Release System into Delayed-Release Systems All double-compressed tablets composed of Eudragits used for outer layer did show the suppression of theophylline release by argon plasma-irradiation, which clearly resulted from decrease in solubility of the outer layer polymers, but the nature of release pattern was different from each other, *i.e.* the theophylline release from L100-55 tablet showed the delayed-release pattern under a certain set of plasma operational conditions. The SEM photographs indicated that surface of outer layer polymers was concurrently softened by plasma heat flux at 50 and 30 W to give a film-like outer layer in addition to the plasma-induced cross-link reactions as an effect of plasma-irradiation. We have then undertaken the measurement of the change in temperature of the tablet surface using "Thermo Label," and the result is shown in Fig. 9. In fact, the temperature of the tablet surface is gradually raised as plasma duration increased, and reached the temperature of higher than T_g point of Eudragit L100-55 within *ca.* 1 min duration at 50 W and *ca.* 3 min duration at 30 W.

A question may arise as to whether or not the delayed-release system can be obtained by having a simple thermal effect on the tablet other than the unique combined effects by plasma-irradiation. We have carried out a heat-treatment of the double-compressed tablet of Eudragit L100-55 at 150 °C for 5 min under atmospheric pressure in argon, and the theophylline release profiles of the resultant tablets are shown in Fig. 10, together with the SEM photo of the tablet surface. Clearly, a simple heat-treatment of the tablet did not lead to an effective suppression of theophylline release due to lack of surface cross-link reaction so as to cause the decrease in solubility of Eudragit L100-55 used for the outer layer, although the SEM photo of the tablet thus treated is superficially similar to that plasma-irradiated for 5 min at 30 W.

Thus, it can be considered that Eudragit L100 and S100 can undergo the inter-segmental cross-link reaction, preferentially in each of powder particles used for the tableting due

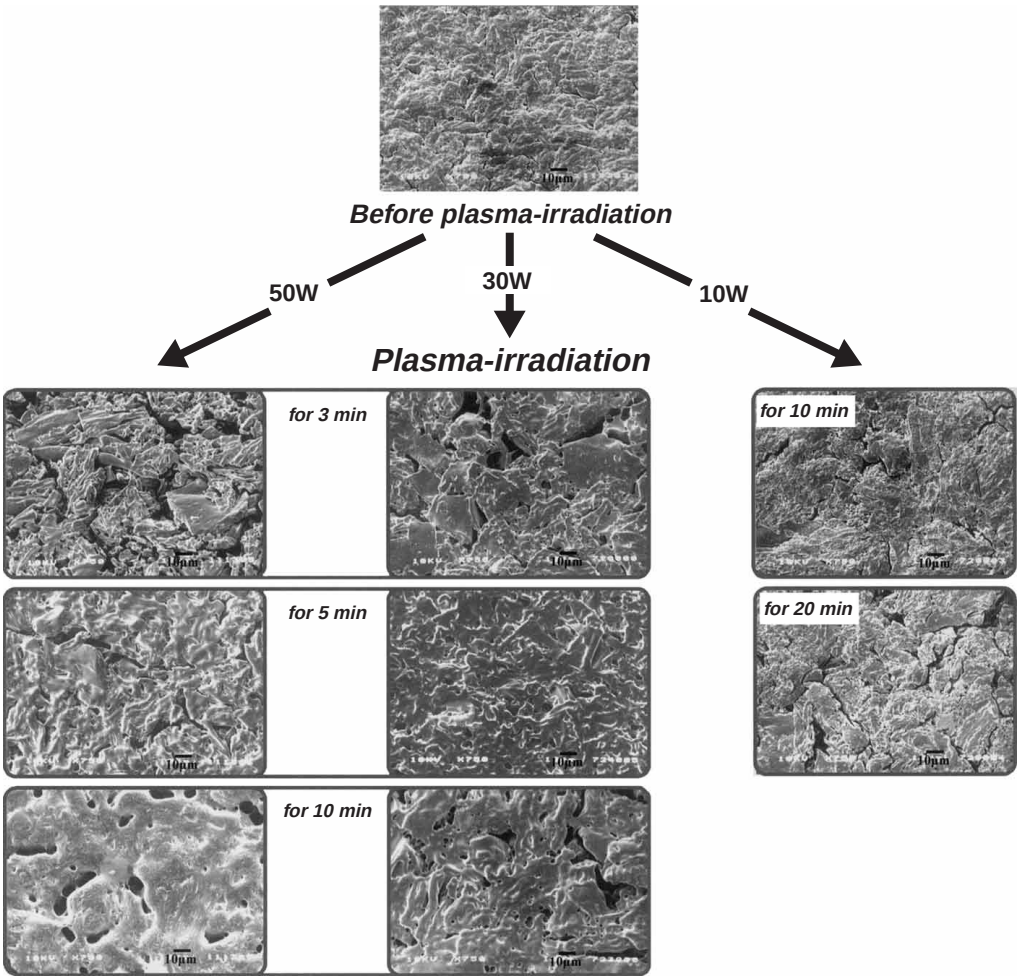


Fig. 8. SEM Photos of Double-Compressed Tablet of Eudragit L100-55 before and after Argon Plasma-Irradiation for 3, 5, and 10 min with Various Plasma Powers

Plasma conditions: Ar 0.5 Torr, 50 ml/min. SEM magnification: ×750.

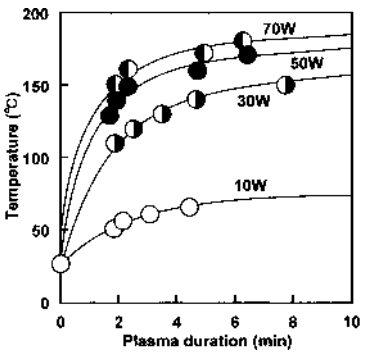


Fig. 9. Change in Temperature of Tablet Surface on Argon Plasma-Irradiation of Supplied Power of 10—70 W for Various Duration

to a weaker interaction at particle–particle interfaces than the intra-particle interaction of polymer segments. However, the decomposition at part of such polymers also concurrently occurred to result in the formation of micropores on the outer layers accompanied by the weight loss of the tablets. Thus, the theophylline was slowly released through the resulting micropores without exhibiting a significant lag-time and changed into a rapid-release when a fluid has soaked into the core theophylline tablet resulting in the swelling enough to break the outer layer of the central part of tablet as visually observed on the theophylline release test. On the other hand, it became clear that Eudragit L100-55 underwent the intersegmental cross-link reaction not only the intra-particle manner but also the particle–particle cross-link reaction due to rapid softening of polymer surface caused by plasma heat flux resulting in the formation of particle–particle interlinked surface. Thus, when Eudragit L100-55 is used as a wall material of the double-compressed tablet, the initial drug release has been completely sustained for a certain period of time, being converted into the delayed-release system. However, it has been shown that the tablet surface has converted into the porous outer layer with a longer plasma-irradiation by physical actions such as evolved gas scattering due to the plasma-induced heat fusion. The tablet thus irradiated showed a very slow release pattern without having a prolonged lag-time.

Conclusion

This paper is the first to deal with an attempt to control the drug release from a double-compressed tablet containing theophylline core by regulating the solubility of pH-dependent water-soluble polymers, Eudragit L100, S100 or L100-55, used as a wall material, and to prepare a completely soluble controlled-release delivery system (DDS) with the outer

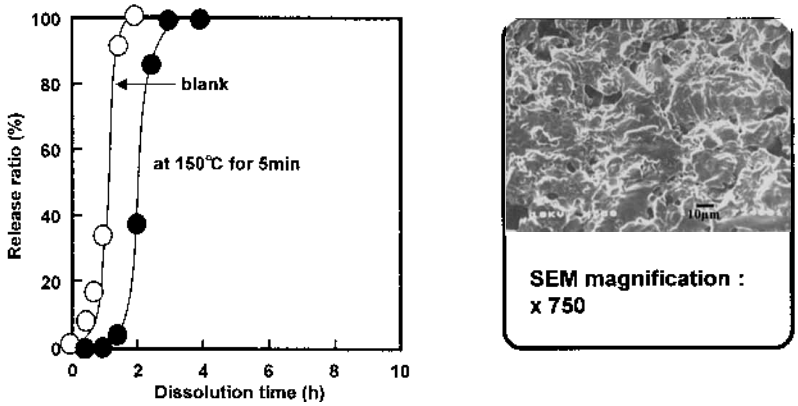


Fig. 10. Effect of Heat-Treatment of Double-Compressed Tablet of Eudragit L100-55 on Theophylline Release, and SEM Photo of the Tablet Surface after Heat-Treatment at 150 °C for 5 min

layer being practically used for pharmaceutical aids by making use of plasma techniques.

We have shown that the rapid theophylline release from a double-compressed tablet of Eudragit L100-55 can be converted into a delayed-release tablet, which is applicable for a time-controlled release system, by selecting a set of conditions of plasma-irradiation and tablet preparations. It was concluded that concurrent occurrence of intra-particle cross-link reaction and polymer-softening leading to particle–particle interlinking has resulted in conversion of rapid-release system into delayed-release system.

The present result provided a basis for the future experimental design to achieve an desired drug release pattern from double-compressed tablets and a criteria for selecting polymers for the outer layer. It is hoped that more refined insight into the scope and limitation will be gained in the course of study now in progress to establish the relationship between a period of lag-time and plasma operational conditions.

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