Development of Patient-Tailored Drug Delivery System by Plasma Techniques

Yasushi Sasai, Yusuke Sakai, Tomoya Nakagawa, Shin-ichi Kondo, and Masayuki Kuzuya*

Laboratory of Pharmaceutical Physical Chemistry, Gifu Pharmaceutical University,
5-6-1 Mitahora-Higashi, Gifu 502-8585, Japan
kuzuya@gifu-pu.ac.jp

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For the most suitable drug therapy, development of controlled-release systems for drug delivery have been thus far investigated for oral application. However, it is difficult for all patients to obtain the expected therapeutic effects of drugs administered due to the individual difference in the environment such as pH value and the transit time in gastrointestinal (GI) tract, which causes the slippage of time-related and positional timing of drug release. From a viewpoint of the real optimization of drug therapy, the Patient-Tailored Drug Delivery System (Tailor-Made DDS) should be developed and administered based on the diagnosis of each patient’s GI environment.

Over the years, we have been working on the structural characterizations and their reactivity of plasma-induced surface radicals of a wide variety of polymers, synthetic and natural, as studied by electron spin resonance (ESR) coupled with the systematic computer simulations. Based on the findings from a series of such studies, we have developed plasma-assisted preparation of double-compressed tablets applicable to oral DDS for sustained- and delayed-release, being derived from the nature of radical formation and radical reactivity.

In a previous paper, when the methacrylic acid-ethylacrylate copolymer, commercially known as Eudragit L100-55 (EL), was used as a single wall material of double-compressed tablet, the drug release has been controlled by occurrence of the surface cross-link reaction by Ar plasma irradiation leading to suppression of the tablet surface solubility since EL contains a plasma-crosslinkable acrylic monomer as one of the components. The double-compressed tablets thus prepared were applicable to time-controlled release systems having a desired lag-time by selecting the plasma operational conditions.

In this communication, we report an extended work of the development of time-controlled DDS with plasma techniques, aiming at the development of "Patient-Tailored DDS" targeting the large intestine.

A mixture of EL and ethylacrylate-methylmethacrylate-trimethylammonioethylmethacrylate copolymer (7:3), commercially known as Eudragit RS (E-RS), was used as an outer layer of double compressed tablet, with expectation of producing the longer lag-time for a drug release since E-RS is pH-independent water-insoluble polymer, and contains a plasma-crosslinkable acrylic monomer as well as EL.

Figure 1 shows the structures of EL and E-RS. EL is one of the pharmaceuticals widely used as enteric coating material and dissolves at higher than pH 5.5. The preparation of double-compressed tablet is essentially the same as methods reported previously.

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\begin{align*}
\text{Eudragit L100-55 (EL)} & \quad \text{Eudragit RS (E-RS)} \\
\text{(soluble at pH>5.5, } T_e = \text{ca. } 110^\circ C) & \quad \text{(insoluble in water, } T_e = \text{ca. } 60^\circ C) \\
\end{align*}
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Fig. 1 Structures of EL and E-RS.
Figures 2 and 3 illustrate the experimental setup for plasma irradiation on tablet and drug dissolution tests, respectively. In this study, we used He plasma instead of Ar plasma, which enables us to carry out surface treatments at the lower temperature than Ar plasma. The drug release properties were evaluated with rotating basket method and flow-through cell method.

We have examined the effect of He plasma-irradiation on release properties of theophylline as a model drug from the double-compressed tablets plasma-irradiated with various supplied powers, 10, 30 and 50 W. Figure 4 shows the results of drug dissolution test in pH 6.8 test solution by rotating basket method. The values shown in Fig. 4 denote the plasma duration.

It is clearly seen that the lag-time for drug release was prolonged as He plasma duration increased, especially for the tablet plasma-irradiated at 30 and 50 W. The result is associated with the presence of a plasma-crosslinkable part in the main of EL and E-RS.

With a view of gaining an insight into the factor to control the lag-time, the changes in the surface characteristics of the plasma-irradiated tablets were monitored by scanning electron microscope (SEM). Figure 5 shows the SEM photos with effect of plasma duration on the progressive changes in the surface morphologies at the plasma powers of 10, 30 and 50 W.

As is clear from Fig. 5, the effect of plasma duration on changes of surface morphology varied with plasma-supplied powers and the softening of tablet surfaces plasma-irradiated at 30 and 50 W progressed with the prolongation of plasma duration. On the other hand, the distinct softening area was not seen on the tablet surface plasma-irradiated at 10 W. These results are apparently derived from heat-effect of plasma irradiation. Thus, we examined the progressive changes in

![Flow Through Cell Method Diagram](image)

**Fig. 3 Experimental setup for dissolution test.**

![Dissolution Ratio Graphs](image)

**Fig. 4 Effect of He plasma-duraiton on drug release properties from double-compressed tablet. Plasma conditions: He 0.5 Torr, 50 mL/min.**
temperature in the plasma reactor using fiberoptic thermometer and the result is shown in Fig. 6. Considering the $T_s$ of EL (ca. 110 °C) and E-RS (ca. 60 °C), it can be reasonably assumed that the partial softening area of tablet surface should be generated mainly from E-RL on plasma irradiation at 30 W (Fig. 5), and from both EL and E-RS on plasma irradiation at 50W. Thus, it became clear that the plasma irradiation caused to form the continuous surface layer, the particle-particle being inter-linked by plasma heat flux and the concomitant occurrence of plasma-induced cross-link reaction resulted in producing a prolonged lag-time for drug release.

In order to evaluate the nature of the drug release from double-compressed tablet thus prepared in the GI tract, we fabricated an experimental setup for the simulated GI tract by use of flow-through cell method (see Fig. 3), the test solution being changed in pH value corresponding to stomach (pH 1.2), small intestine (pH 7.4) and large intestine (pH 6.8). It is well known that gastric transit time of pharmaceuticals orally administered varies the time from 15 min to more than 3h. On the other hand, the transit time in small intestine is relatively constant (3-4h). Thus, the flow duration of pH 1.2 test solution was varied in this experiment. Figure 7 shows the result of dissolution test by flow-through cell method.

It can be seen from Fig. 7 that the lag-time increased with the extension of plasma irradiation time in the simulated GI environment. One of noteworthy points in Fig. 7 is that the lag-time was not largely affected by treatment in pH 1.2 test solution. The result indicates that the double compressed tablets thus prepared are applicable to a GI tract targeting for drug delivery by the plasma-assisted control of lag-time without affecting the variation of the gastric resistance time of tablet orally administered.

The present result provided a basis for the development of “Patient-Tailored DDS” by plasma techniques. It is hoped that more precise insight into the scope and limitation will be gained in the course of study now in progress to establish the relationship between a lag-time for drug release and plasma operational conditions.
Fig. 7 Release properties of theophylline from He plasma-irradiated double compressed tablets in simulated GI tract: A: for 1 hr in pH 1.2, B: for 4 hr in pH 1.2. Plasma conditions: He 0.5 Torr, 50mL/min.

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