Preparation of Floating Drug Delivery System by Plasma Technique

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A novel intragastric floating drug delivery system (FDDS) has been prepared by pulsed plasma-irradiation on the double-compressed tablet of 5-Fluorouracil (5-FU) as a core material with outer layer composed of a 68/17/15 weight ratio of Povidone (PVP), Eudragit RL (E-RL) and NaHCO₃. The plasma heat flux caused the thermal decomposition of NaHCO₃ to generate carbon dioxide and the resultant gases were trapped in bulk phase of outer layer, so that the tablets turned to have a lower density than the gastric contents and remained buoyant in simulated gastric fluid for a prolonged period of time. In addition, the release of 5-FU from the tablet is sustained by occurrence of plasma-induced crosslink reaction on the outer layer of tablet and the release rate of 5-FU can be well controlled by plasma operational conditions.

Key words pulsed-plasma technique; double-compressed tablet; floating drug delivery system; poly(N-vinylpyrrolidone); Eudragit; sodium dicarbonate

Oral drug delivery is the most desirable and preferred method of administering therapeutic agent for their systematic effects such as patient acceptance, convenience in administration, and cost-effective manufacturing process. Thus, a wide variety of approaches of drug delivery system (DDS) have been investigated for oral application. However, the development process is precluded by several physiological difficulties, such as an inability to restrain and localize the DDS within desired regions of gastrointestinal tract and highly variable nature of gastric emptying process. For example, the relatively brief gastric emptying time (GET) can result in incomplete drug release from the DDS devices leading to diminished efficacy of the administered dose.

Intragastric floating drug delivery system (FDDS) is noted as one of the orally applicable DDS for prolongation of the GET. The bulk density of FDDS is lower than that of gastric fluids and thus it remains buoyant on stomach contents for a long time in the drug releasing process. Hence, it is useful for obtaining the sufficient bioavailability and the effective “plasma” level, especially for drug having limited absorption sites in the upper small intestine, such as furosemide, ketoprofen. In addition, FDDS is one of the optimal systems for stomach mucosa targeting of antitumor agent for the treatment of stomach cancer and antibiotics for the eradication of Helicobacter pylori. However, with most of FDDS devices developed previously, it is difficult for all patients to obtain the expected therapeutic effects of drug administered, since the drug is released with a pattern programmed in the manufacturing process despite individual differences in stomach such as pH value and the transit time in gastrointestinal tract. Thus, from a viewpoint of the real optimization of drug therapy, the drug release properties of FDDS should be adjusted to individual stomach conditions.

Over the years, in a series on preparation of double-compressed (DC) tablets for use in a DDS with plasma techniques, we have reported that novel sustained- and delayed-release systems can be prepared by plasma-irradiation on the outer layer of DC tablet as well as matrix-type composite powder for sustained-drug release system can be prepared by mechanically-amplified plasma processing. During the course of such studies on plasma-assisted DDS preparation, we have found that the carbon dioxide was trapped in the tablet when argon plasma was irradiated onto the DC tablet composed of plasma-crosslinkable polymers possessing carboxyl group as an outer layer. Since such tablets turned to floating system on the water, it was considered that this could be applicable to FDDS. In fact, we have obtained the intragastric FDDS by plasma-irradiation on DC tablet using a mixture of methyl vinyl ether–maleic acid copolymer (VEMAC) and hydroxypropylmethylcellulose phthalate (HPMCP) with plasma-crosslinkable properties as outer layer. The tablet thus plasma-irradiated had a floating ability in simulated gastric fluid and the drug release from tablet could be controlled at a desired rate by selecting plasma operational consitions.

Based on the findings obtained from plasma-assisted FDDS preparation with VEMAC, we examined the possibility of preparation of DC tablet of 5-fluorouracil (5-FU) with outer layer using polymers approved as pharmaceutical aids, water-soluble poly(N-vinylpyrrolidone) (PVP) and water-insoluble ethylacrylate–methylmethacrylate–trimethylaminoethylmethacrylate chloride copolymer (E-RL), commercially known as Povidone and Eudragit RL, respectively. Figure 1 shows the structures of PVP and E-RL. They are classified as plasma-crosslinkable polymers because of presence of typical plasma-crosslinkable monosubstituted vinyl monomers in the component. And, NaHCO₃ powder was added to the outer layer with expectation that evolved gases generated by plasma-induced thermal decomposition of NaHCO₃ would be effectively trapped in the bulk phase of outer layer, leading to decrease in density of the tablet.

We report here the detailed account of the preparation of such a FDDS by plasma techniques.
Experimental Materials

Commercial PVP (MW = ca. 30000, Wako Pure Chemical Industries, Ltd., Japan), E-RL (MW = 150000, Rohm Pharma, Germany, distributed by Higuchi Shoukai Co., Japan) and NaHCO₃ (Nakarai Tesque Inc., Japan) were used as outer components of double-compressed tablet. These were screened through prescription mesh sieves and dried in vacuo for 24 h before use. The glass transition temperature (Tg) was ca. 150 °C for PVP, and ca. 60 °C for E-RL, respectively. NaHCO₃ are rapidly decomposed at 150 °C to generate carbon dioxide. Commercial 5-Fluorouracil (5-FU) (Tokyo Kasei Co., Ltd., Japan) was used as a model drug. It was dried at 60 °C in vacuo for 24 h, and used without further purification.

Preparation of Double-Compressed (DC) Tablet

The DC tablet was obtained as follows: a flat-faced core 5-FU tablet (50 mg, 8 mm in diameter) was first prepared at a pressure 40 kg/cm² (3.92 MPa) for 10 s, then the core tablet was placed onto half of the prescribed amount of powdered component (75 mg of the fractions screened with a 140—200 mesh sieve) as a wall tablet was placed onto half of the prescribed amount of powdered component (75 mg) was placed in the core tablet, the whole was compressed at pressure of 200 kg/cm² (19.62 MPa) for 30 s. All flat-faced tablets were prepared using hand press instrument (SSP-10A, Shimadzu Co., Japan).

Continuous Wave- and Pulsed-Plasma Irradiation

A schematic representation of the apparatus for plasma-irradiation is shown in Fig. 2, and this apparatus is essentially the same as reported earlier. The plasma state was generated by the use of radio frequency discharges of inductive coupling with supplied power of 70 and 100 W at 13.56 MHz. Flow volume (50 ml/min) and pressure of argon gas (0.5 Torr (66.7 Pa)) for plasmosynthesis were controlled by flow meter and changing evacuating speed, respectively. The sample tablets were placed on a glass-tripod in reaction chamber to ensure homogenous exposure to plasma. Pulsed-plasma irradiation was carried out according to the method similar to the above using the radio frequency generator connected with a pulse generator under the prescribed plasma on and off pulse widths in the millisecond range as duty cycle (equivalent power 70 W = 35 ms-On/35 ms-Off)×peak power 100 W). The temperature in plasma reaction chamber was measured by fiber optic thermometer (FL-2000, Anritsu Meter Co., Ltd., Japan).

Test of 5-FU Release

The 5-FU release from the plasma-irradiated DC tablet was evaluated according to the paddle-beads method, which assumes the mechanical impact force received in stomach. In this experiment, 1500 polystyrene beads (diameter, 6.35 mm; specific gravity, 1.05 g/cm³) in 300 ml of pH 1.2, 3.0 and 5.0 solution were used. The rotation speed of paddle was set at 75 rpm for all the dissolution tests. Released 5-FU was periodically assayed by absorption spectrum (UV-1700, Shimadzu Co., Japan) at the wave-length of 265 nm.

Scanning Electron Microscopy

The microscopic morphological changes in the surface and the vertical section of plasma-irradiated DC tablet were photographed by scanning electron microscope (SEM) (JSM-330A, JEOL Ltd., Japan) with accelerating voltage of 10 kV.

Density Measurement of Tablet

The density of plasma-irradiated DC tablet was determined by the liquid displacement method using n-hexane as a displacement liquid.

Results and Discussion

Plasma Operational Conditions for FDDS Preparation

The plasma-induced heat effect is one of the most important factors for the preparation of FDDS with plasma techniques because the floating ability of DC tablet results from decreasing in density of tablet coupled with a thermal decomposition of NaHCO₃ in bulk phase of outer layer. Thus, in order to determine the suitable plasma conditions of both CW- and pulsed-plasma for this FDDS preparation, the temperature in plasma reactor was monitored using fiber optic thermometer.

Figure 3 shows the progressive changes in temperature in the plasma reaction chamber during continuous wave (CW)-plasma irradiation at supplied powers of 100 and 70 W, and pulsed-plasma irradiation at supplied power of 100 W with the duty cycle of 0.7 (35 ms on and 15 ms off) equivalent to average power input of 70 W. When the CW argon plasmas were irradiated onto a tablet under the present operational conditions, the temperature in plasma reactor was gradually raised as plasma duration increased, and almost reached 200 °C at 20 min duration even at the power of 70 W. In these cases, the drugs available for a core tablet would be restricted to some thermo-stable substances.

On the other hand, it is clearly seen that the temperature rise is markedly suppressed in case of pulsed-plasma irradiation and the temperature in the plasma reactor leveled off at ca. 150 °C, which is a high enough temperature to cause the decomposition of NaHCO₃. This result suggests that pulsed-plasma techniques are useful for controlling the temperature rise in the reaction chamber accompanied with a thermal effect of plasma by selecting duty cycle. Thus, from a viewpoint of minimizing plasma-induced thermal damages to the core drug, we used a pulsed argon plasma-irradiation at supplied power of 100 W with the duty cycle of 0.7 for FDDS preparations in this study.

Floating and 5-FU Release Properties of Pulsed-Plasma Irradiated DC Tablet with Outer Layer of PVP or E-RL Containing NaHCO₃

In order for a dosage form to float in the stomach, the density should be less than that of the gastric contents, reported as 1.004 g/cm³. We first carried out pulsed argon plasma-irradiation on DC tablets with outer layer of PVP or E-RL containing a various weight ratio of NaHCO₃ to determine the suitable NaHCO₃ ratio in outer layer.

Figure 4 shows the results of the density measurement of DC tablets with outer layer of PVP or E-RL containing various weight ratio of NaHCO₃ (0—50 wt%) after pulsed-plasma irradiation for 10 min. The values shown in parenthe-
tablet with outer layer composed of E-RL and NaHCO₃ for other hand, when the pulsed-plasma was irradiated on the DC gases generated by the decomposition of NaHCO₃ leave from tendency to level off with a higher ratio of NaHCO₃ unlike tablet decreased within 15 wt% of NaHCO₃, but they had a 10 min, the measured densities and weight losses of DC 15 wt% of NaHCO₃ are expected to have a good floating property in gastric fluid.

ses present the average weight loss (mg, n=3) of tablet after plasma-irradiation.

As shown in Fig. 4, when PVP was used as polymer, the plasma-irradiated DC tablet with outer layer composed of PVP and 15 wt% of NaHCO₃ had a minimum density of 0.880 g/cm³ although the weight of the tablet decreased as the ratio of NaHCO₃ increased. This result suggests that the gases generated by the decomposition of NaHCO₃ leave from bulk phase of outer layer without being sufficiently trapped when the NaHCO₃ ratio in outer layer is over 15 wt%. On the other hand, when the pulsed-plasma was irradiated on the DC tablet with outer layer composed of E-RL and NaHCO₃ for 10 min, the measured densities and weight losses of DC tablet decreased within 15 wt% of NaHCO₃, but they had a tendency to level off with a higher ratio of NaHCO₃ unlike the tablet composed of PVP. These results suggest that the plasma-irradiated DC tablets with outer layer containing 15 wt% of NaHCO₃ are expected to have a good floating property in gastric fluid.

Figure 5 shows the release properties of 5-FU as a model drug from the pulsed-plasma irradiated DC tablets with outer layer of PVP or E-RL containing 15 wt% of NaHCO₃ by paddle-beads method in simulated gastric solution (pH 1.2 buffer solution), and the photos of each tablet during dissolution test. All the plasma-irradiated tablets had floating abilities in test solution although non-plasma irradiated tablets sank immediately.

It can be seen from Fig. 5 that the 5-FU releases from the DC tablet of PVP are sustained to some extent by pulsed-plasma irradiation, compared with the non-plasma irradiated tablet. The result clearly stems from the occurrence of the cross-link reactions on the tablet surface by plasma irradiation. However, as shown in the photo of the tablet in 5-FU dissolution process, the mechanical strength of outer layer of PVP containing 15 wt% of NaHCO₃ was inadequate due to high water-solubility of PVP and the outer layer was gradually disintegrated by the mechanical impact forces received from beads, so that prolonged sustained release of 5-FU was not observed even when plasma duration was prolonged to more than 20 min.

On the other hand, unlike the tablets of PVP, the plasma-irradiated DC tablets of E-RL have floated on the test solution without disintegrating in the 5-FU dissolution process by paddle-beads method and exhibited very slow release patterns although non-plasma irradiated tablet have completely released 5-FU within 2h due to the disintegration of outer layer. Since the $T_g$ point of E-RL, ca. 60 °C, is much lower than the temperature of plasma gases, the E-RL particles in outer layer would be softened by plasma heat flux to form a particle-particle interlinking, leading to the formation of film-like continuous layer. As the results, it was considered that the mechanical strength of outer layer was improved and the 5-FU release changed into such slow patterns because the test solution should penetrate through a continuous layer of E-RL into core drug. Also, the rate of 5-FU release from plasma-irradiated tablets of E-RL decreased as plasma duration increased, suggesting the occurrence of plasma-cross link reaction on tablet surface.

**FDDS Preparation by Pulsed-Plasma Irradiation on DC Tablet with Outer Layer of a Mixture of PVP and E-RL Containing NaHCO₃** In order to prepare FDDS with desired drug release properties and floating abilities by plasma-irradiation, the effect of pulsed-plasma irradiation on the DC tablet with outer layer of a mixture of PVP and E-RL containing 15 wt% of NaHCO₃ was examined.

Table 1 and Fig. 6 show the each formulation of outer layer composed of various ratio of PVP/E-RL and 5-FU release properties from pulsed-plasma irradiated each tablet at supplied power of 100 W with the duty cycle of 0.7 for various durations, respectively. All the plasma-irradiated tablets floated on the pH 1.2 test solution and retained its shape without disintegrating during the dissolution test by paddle-beads method. Thus, they are expected to have suitable floating properties and mechanical strengths for intragastric FDDS.

As can be seen from Fig. 6, all the tested tablets were con-
verted into the sustained-release system by pulsed-plasma irradiation. And, the effects of plasma-duration on the release rate of 5-FU were remarkably observed in double-compressed tablet with outer layer of Formulation IV, a 68/17/15 weight ratio of PVP, E-RL and NaHCO₃. This result suggests that the 5-FU release from DC tablets with outer layer of Formulation IV can be controlled at a desired rate by selecting the plasma operational conditions.

Figure 7 shows the changes in the density of DC tablet with outer layer of Formulation IV on plasma duration. Values shown in parentheses present the weight loss (mg) of tablet after plasma-irradiation. Plasma conditions: 100 W, duty cycle 0.7 (on/off 35 ms/15 ms), 66.7 Pa, Ar 50 ml/min. Each point represents the mean ± S.D. (n = 3).

Figure 7. Changes in the Density of Pulsed-Plasma Irradiated DC Tablet with Outer Layer of Formulation IV on Plasma Duration

outer layer of plasma-irradiated DC tablet. Figure 8 shows the SEM photos of the surface and the vertical section of DC tablet with outer layer of Formulation IV before and after plasma-irradiation for 10 min. In fact, as can be seen from Fig. 8, the surface and bulk phase of outer layer partially softened to form particle–particle interlinking and many micro-pores produced by thermal decomposition of NaHCO₃ were observed in the bulk phase of outer layer after plasma irradiation. Considering the temperature in plasma reaction chamber as shown in Fig. 3, it can be assumed that the softened areas of plasma-irradiated tablet mostly stems from E-RL having a relatively low \( T_g \) temperature.

Separately, we have carried out heat treatments of the DC tablet at 150 °C for various duration, and the 5-FU release profiles of the resultant tablets are shown in Fig. 9. Clearly, such a simple heat treatment of the tablet did not lead to an effective controlled release of 5-FU due to lack of surface cross-link reaction, although the floating on simulated gastric fluid was observed. Thus, it can be concluded that the con-
trolled release of 5-FU from DC tablet with outer layer of Formulation IV has been achieved by the occurrence of plasma-induced cross-link reaction on the tablet surface.

**Effect of pH on 5-FU Release from Plasma Irradiated DC Tablet** It has been reported that the pH value of gastric fluid can increase to as high as pH 3—5 in the fed state. Thus, we have also examined the 5-FU release profiles from pulsed-plasma irradiated DC tablet with outer layer of Formulation IV in pH 3.0 and 5.0 buffer solution, and the results are shown in Fig. 10.

As shown in Fig. 10, the 5-FU release rates varied somewhat with pH. This result stems from the fact that water permeability of outer layer of DC tablets changes with buffer solution because the water permeability of E-RL in outer layer of DC tablet strongly depends on anionic species and concentration in buffer solution rather than the pH value. However, it can be seen that well-controlled 5-FU releases are achieved by plasma duration under the present conditions without strongly affecting pH variations in test solution.

**Conclusion**

The present results have provided a basis for the plasma-assisted FDDS preparation including the criteria for selecting pharmaceutical aids of outer layer and plasma operational conditions. The pulsed-plasma technique was effective to suppress the excessive heat generation and level off at enough temperature to cause the decomposition of NaHCO₃. The plasma-irradiated DC tablets with outer layer composed of a 68/17/15 weight ratio of PVP, E-RL and NaHCO₃ had a good floating property and a suitable mechanical strength, and the rate of 5-FU release from tablet thus prepared was well-controlled by selecting the operational conditions for pulsed-plasma irradiation without strongly affecting the pH variations of test solution. It was concluded that both properties of the tablet, flotation in simulated gastric fluid and sustained drug release, have been achieved by the combined effect of plasma heat flux leading to thermal decomposition of NaHCO₃ in bulk phase and the concomitant occurrence of plasma-induced cross-link reaction on the tablet surface.

It is hoped that the FDDS applicable to the drug therapy adjusted to individual stomach conditions, such as the GET and the pH-variation, with plasma techniques will be developed in the course of work now in progress to establish the relationship between a drug release pattern and a plasma operational condition.

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