Development of Drug Delivery System by Atmospheric Pressure Glow Plasma

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1. Introduction

Surface treatments with cold plasma are being utilized for an ever-increasing number of applications and have many advantages for modification of materials. In view of the fact that surface reactions of plasma treatment are initiated by plasma-induced surface radicals, 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 drug delivery system (DDS) for sustained- and delayed-release.

In a previous paper, we reported the preparation of time-controlled drug release system by He plasma-irradiation to the double-compressed tablet having a mixture of methacrylic acid-ethylacrylate copolymer, commercially known as Eudragit L100-55 (EL), and ethylacrylate-methylmethacrylate-trimethylaminoethylmethacrylate copolymer, commercially known as Eudragit RS (ERS), as an outer layer (schematically illustrated in Fig. 1). The double-compressed tablet thus prepared showed drug release after a time of non-release (lag time), and the lag time can be controlled by selecting plasma operational conditions since it is prolonged by occurrence of plasma-induced cross-link reaction on tablet surface.

On the other hand, cold plasma of homogeneous glow discharge had been thought to be stable only in a low pressure of the order of less than a few Torr. However, the atmospheric pressure glow (APG) plasma which the stable and homogeneous glow discharge were generated even at atmospheric pressure has recently been developed. Today, the APG plasma technique has actually received an intense interest in a wide variety of industrial applications, due to its low apparatus and running cost compared with the low-pressure plasma.

As an extended work on DDS preparations by plasma techniques, we examined the usefulness of APG plasma, instead of cold plasma at a low pressure, for more practical use. We report in this communication the preparation of time-controlled drug release system by He plasma-irradiation at 700 Torr to the surface of double-compressed tablet.

2. Experimental

A mixture of EL and ERS (7:3) was used as outer layer of double-compressed tablet. Figure 2 shows the structure of EL and ERS. Both EL and ERS is a plasma-crosslinkable polymer since they

![Time-controlled drug release system](image)

Fig. 1 Conceptional illustration for preparation of time-controlled drug release system by plasma technique.

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contain a plasma-crosslinkable acrylic monomer as one of the components. Theophylline was used as a model core drug. Figure 3 illustrates the schematic representation for preparation of double-compressed tablet. It is essentially the same as used in a previous paper.3

Figure 4 shows the experimental set-up for plasma irradiation on double-compressed tablet. A pair of copper electrodes coated with alumina ceramics (15 cm × 15 cm, gap between electrodes was 1 cm) was connected with high frequency generator with impulse high voltage (Haiden Laboratory Inc.). The double-compressed tablet set in the specially made holder was put on the center of lower electrode.

Test of theophylline release from the double-compressed tablets was conducted in a phosphate buffer solution of pH= 6.8 at 37 ± 0.5 °C according to the standard method for dissolution test (Japanese Pharmacopoeia Fourteenth, Method 1) using a rotational basket apparatus (NTR-3000, Toyama Industry) with rotating speed of 100 rpm. Released theophylline was periodically assayed by absorbed spectrum (UV-1700, Shimadzu Co.) at the wave-length of 270nm.

3. Results and Discussion

We examined the effect of He plasma-irradiation under various pressure (100~700 Torr) on release properties of theophylline from double-compressed tablet. Figure 5 shows the effect of plasma duration on theophylline release profiles from He plasma-irradiated double-compressed tablet at 100 Torr or 700 Torr. The values shown in Fig.5 denote the plasma duration.

It is clearly seen that the lag time was prolonged as He plasma duration increased, and the release patterns of theophylline from double-compressed table plasma-irradiated at 100 Torr and 700 Torr were similar to each other although the effect of plasma duration on prolongation of lag time varied somewhat between irradiation at 100 Torr and at 700 Torr.

In order to understand the factor to control the lag time, the progressive changes in the surface morphology of plasma-irradiated tablet were monitored by scanning electron microscope (SEM). Figure 6 shows the SEM photos with the effect of plasma-irradiation on the progressive changes in the surface morphology. The SEM photos indicated that the surface of outer layer polymers...
Fig. 5 Effect of plasma duration on theophylline release properties form plasma irradiated double-compressed tablet.
Plasma condition: frequency; 3 kHz, voltage; 12 kV, power; 250 W, He gas flow rate; 3 L/min.

was gradually softened by plasma heat flux as plasma duration increased. We have then undertaken the measurement of the changes in temperature of the tablet surface using “Thermo Label” and the result is shown in Fig. 7. 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 ERS within ca. 3 min duration at 700 Torr and ca. 10 min duration at 100 Torr. Thus, it can be reasonably assumed that the partial softening area on tablet surface in Fig. 6 mainly resulted from melting of ERS. Furthermore, the formation of particle-interlinked surface can be clearly seen on the double-compressed tablet plasma-irradiated at 700 Torr for 20 min. This might result from melting of both ERS and EL because the temperature of tablet surface nearly reached the $T_g$ of EL by plasma-irradiation at 700 Torr for 20 min as shown in Fig. 7. Thus, it became clear that the plasma-irradiation caused to form the continuous surface layer by plasma heat flux and the concomitant occurrence of plasma-induced cross-link reaction on tablet surface resulted in producing a prolonged lag-time for drug release. These results indicate that APG plasma irradiation to the surface
of double-compressed tablet leads to the formation of time-controlled release systems with the lag time being readily controlled by plasma operational conditions, similarly in the case of low pressure-cold plasma as reported previously.\(^3\)

The present results provide a basis for further experimental design for DDS preparations using APG plasma and it is hoped that more practical applications will be developed in the course of study now in progress.

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References


