

Preparation and Characteristics of a Novel Sustained and Controlled Release Drug Delivery Device by Plasma Technique

Yukinori Yamauchi¹, Masayuki Kuzuya², Yasushi Sasai³,
Naoki Doi³, and Shin-ichi Kondo³

¹Department of Pharmaceutical Physical Chemistry, College of Pharmaceutical Sciences, Matsuyama University, 4-2 Bunkyo-cho, Matsuyama, Ehime 790-8578, Japan

²Department of Health & Welfare, Chubu Gakuin University, 2-1, Kirigaoka, Seki-shi, Gifu, 501-3993, Japan

³Laboratory of Pharmaceutical Physical Chemistry, Gifu Pharmaceutical University, 1-25-4 Daigaku-Nishi, Gifu 501-1196, Japan

Keywords: Oxygen plasma irradiation, drug delivery system, cellulose derivatives

1. Introduction

Increased complications and expense involved in marketing of new drug entities has focused greater attention on development of sustained and controlled release drug delivery systems [1]. The purpose of the systems is to maintain drug concentration in the blood or in target tissues at a desired value as long as possible. To achieve predictable and reproducible release rates, extended duration of activity for short half-life drugs, decreased toxicity, and reduction of required dose, optimized therapy and better patient compliance, a sustained-release (SR) formulation of various drugs is desirable [2].

Over the years, we have been working on the development of plasma-assisted preparation of multi-layered tablets applicable to oral drug delivery system (DDS) [3-5]. In previous papers, we reported the preparation of SR system by oxygen plasma-irradiation to the double-compressed tablet having a mixture of plasma-crosslinkable material, like polystyrene (PSt) or hydroxypropyl methylcellulose acetate succinate (HPMCAS), and plasma-degradable material, like polyoxymethylene (POM) or lactose, as a wall material [6,7]. When oxygen plasma was irradiated to the outermost layer of the tablet, plasma-degradable material could be selectively eliminated and simultaneously plasma-cross-

linkable material undergoes the rapid crosslink reaction to result in the formation of the porous outer layer of the tablet. As a result, the drugs could be released slowly from the tablet through the resulting micropores.

The objective of this study was to develop once-daily sustained-release dosage forms, which releases drug at zero-order rate with accurate control in the gastrointestinal tract.

2. Experimental

2.1. Materials

HPMCAS (AS-LF, Fig.1) was kindly supplied by Shin-Etsu Chemical Co. (Tokyo, Japan). Lactose monohydrate (Fig.1) was purchased from Wako Pure Chemical Industry Co. (Tokyo, Japan). All other materials used were of analytical grade, and procured from commercial sources.

2.2. Plasma-Irradiation and Tablet Preparation

Tested powders or tablets were treated with radio frequency (13.56 MHz) plasma.

The double-compressed tablets were obtained as follows: a flat-faced core diclofenac sodium tablet (50 mg, 10 mm ϕ), as a model drug, was first prepared at a pressure of 40 kg/cm² for 10 s, and then the core tablet was placed onto half of the prescribed amount of powdered mixture (50 mg) as a wall material in a tablet die. After the

rest of the powdered mixture (50 mg) was placed on the core tablet, the whole was compressed at pressure of 200 kg/cm² for 30 s. All flat-faced tablets were prepared using a hand press instrument in a tablet die (SE work press and SE dice, Okada seiko Co., Japan).

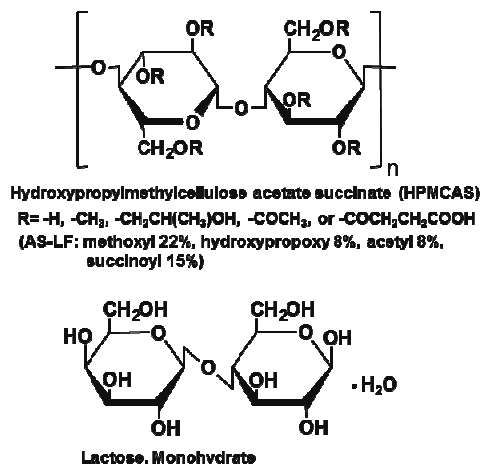


Fig. 1. Chemical structures of HPMCAS and Lactose monohydrate.

The apparatus and methods for plasma-irradiation on both powder and tablet is essentially the same as reported earlier [3-7]. The plasma state was generated by use of capacitively coupled parallel-plate radio frequency discharges at 13.56 MHz with supplied power of 50 W. Flow volume (50 mL/min) and pressure of argon or oxygen gas (66.6 Pa) for plasmolysis were controlled by changing evacuating speed. The sample tablets were placed on a glass-tripod in a reaction chamber (240 mm long, 150 mm ϕ) to ensure homogeneous exposure to plasma gas.

Degradation rate of sample 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.

2.3. Scanning Electron Microscope (SEM)

The microscopic changes in the surface of the plasma-irradiated powders and tablets were evaluated by SEM (S-3400N, Hitachi, Japan) with an accelerating voltage of 5 kV and magnification of x 500–2,000. Prior to the analyses, the samples were sputtered with a thin film of gold.

2.4. In Vitro Release Studies

The in vitro dissolution studies were carried out using a dissolution test apparatus with an

autosampling apparatus (Toyama Sangyo Co., Osaka, Japan) at 100 rpm. The dissolution medium consisted of the 0.1 M phosphate buffer pH 7.4 (900 mL), maintained at 37C \pm 0.5°C. The drug release at different time intervals was measured by a Shimadzu UV-1800 spectrometer (Shimadzu Inc., Kyoto, Japan) at 270 nm using UV system ver.3.2 software (Toyama Sangyo Co., Osaka, Japan). It was made clear that none of the ingredients used in the formulations interfered with the assay. The release studies were conducted in triplicate, and the mean values were plotted versus time.

3. Results and Discussion

3.1. Plasma treatment of HPMCAS powder

We have already undertaken plasma irradiations on several cellulose derivatives such as EC, HEC, HPC, CMC, Chitin and Chitosan, and the radicals formed were studied by ESR with the aid of systematic computer simulations [8-10]. Based on a series of such studies, it was found that the surface of plasma-irradiated cellulose derivatives can be consisted of dangling-bond sites as a major component radical, indicative of the concurrent occurrence of the cross-link reaction in addition to a degradation reaction of cellulose main chain initiated by the 1,4-glucoside bond scission. Likewise, HPMCAS, including highly plasma-crosslinkable side chain contained as a major substituent, can be assumed to form a cross-linked layer on the surface by plasma irradiation.

To determine the morphology changes induced by the plasma treatment, the surface of non-treated and treated HPMCAS powder were analyzed with SEM. It can be seen clearly from Fig. 2(a) that the particle size distribution of original HPMCAS powders is uniform in the size range of 2–5 μ m. In the case of plasma treated samples, several agglomerates can be observed and also their average size was determined to be 20–70 μ m (Fig. 2(b)).

3.2. Degradation Property of HPMCAS by Plasma-Irradiation

The degradation property of materials by plasma irradiation is known to be dependent on the plasma reaction apparatus and shape of the samples. In order to understand the nature of plasma-irradiation effect on degradation of non-treated and treated HPMCAS, we therefore studied the plasma degradation property of samples focusing on the changes in the weight

loss of the directly-compressed tablets by plasma irradiation. Figure 3 illustrates changes in the weight loss according to the oxygen plasma irradiation time in comparison with the results obtained with typical cross-linkable PSt and degradable POM and lactose.

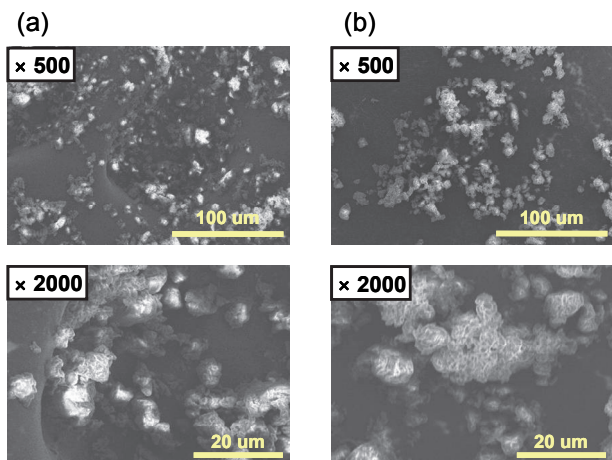


Fig. 2. SEM images of HPMCAS powders (a) before and (b) after plasma-irradiation. Plasma condition: 50 W, Ar 50 mL/min, 66.6 Pa.

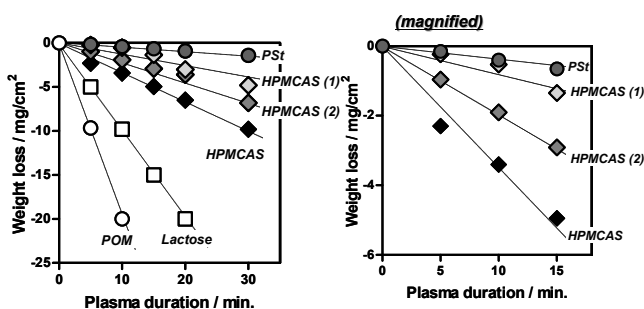


Fig. 3. Effect of oxygen plasma-irradiation on the degradation of flat-faced compressed tablets consisted of various compounds. HPMCAS(1): Ar plasma pretreatment (10 W, 10 min) HPMCAS(2): Ar plasma pretreatment (20 W, 10 min) Plasma condition: 50 W, O₂ 50 mL/min, 66.6 Pa.

It is seen that degradation rate of the treated HPMCAS are all lower than that of non-treated sample. This indicates that the cross-linked layer formation on the surface of HPMCAS powder by argon plasma pretreatment is effective to protect against oxidative decomposition with oxygen plasma irradiation.

Based on the fact that the value of weight loss increases as the plasma duration increases, it seems apparent that plasma degradable lactose could be selectively eliminated to result in the formation of the porous outer layer of the tablet. Then, drug could be released from the tablet through the resulting micropores.

3.3 Diclofenac Release from Plasma-Irradiated Double-Compressed Tablets

The two types of double-compressed tablets containing diclofenac sodium as a core material (50 mg, 10 mm in diameter) and mixture of pretreated or non-pretreated HPMCAS and lactose in 9:1 by weight as a wall material (mixture 100 mg, 13 mm in diameter) were prepared. Subsequently, dissolution tests of the oxygen plasma-irradiated and non-irradiated tablets were carried out using the rotating basket apparatus method. Figure 4 illustrates the dependence of the release property of drug in a buffer solution at pH 7.4 from the tablets on the plasma irradiation time. As is clear in Fig. 4, oxygen plasma non-irradiated tablet (blank) showed quick disintegration and burst release of drug at the very beginning due to combined effects of water absorption and swelling by the formulation. On the other hand, all the tablets plasma-irradiated for more than 5 min have clearly shown no burst release due to conversion into a sustained-release tablet. Moreover, the tablets consisted of pretreated HPMCAS gave a slower and continuous release profile over 8 h and showed near zero-order kinetics until approximately 50–70% of the drug in the tablet was released.

Thus, when the combinations of pretreated HPMCAS–Lactose (9:1) are used as a wall material of the double-compressed tablet, the plasma-irradiated tablets provided long term and stable drug release. It could be considered that the present tablets are apparently applicable to controlled-release systems having a desired release kinetic pattern by optimizing the plasma operational conditions.

The surface characteristics of the tested tablets were monitored by SEM observations. Figure 5 presents several SEM images on the surface of double-compressed tablets of pretreated- or nonpretreated-HPMCAS–Lactose, before and after plasma-irradiation for 10 min. In comparison with surface of the blank tablet, the plasma-irradiated tablets have taken on very rough structure.

It is apparent that plasma irradiation caused cross-link reaction of HPMCAS, resulting in the formation of a non-uniform crosslinked barrier. Furthermore it is clearly seen that plasma-irradiation generate a number of micropores due to the oxidative decomposition and/or vaporization of lactose monohydrate, resulting in

the formation of the porous outer layer. It was also shown that the formation of fine-micropores with an approximate size of 2–10 μm can be successfully achieved on the tablet consisted of argon plasma pretreated HPMCAS, as shown in

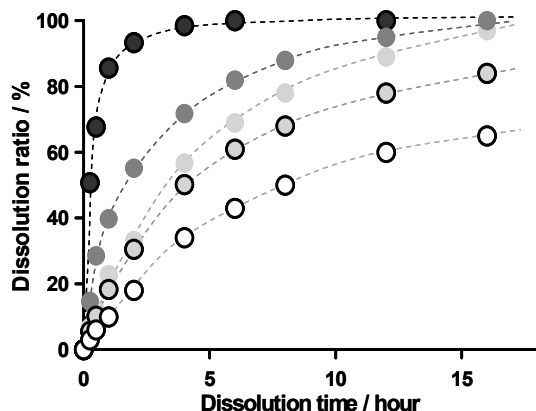


Fig 4. Effect of plasma durations on diclofenac release properties in pH 7.4 buffer solution from plasma-irradiated double-compressed tablets using powdered mixtures of HPMCAS–Lactose (9:1) as outer layer.

Plasma conditions: 50 W, O₂ 50 mL/min, 66.6 Pa.
 ●, blank; ●, 5 min duration (non-pretreatment); ●, 10 min duration (non-pretreatment); ○, 10 min duration (Ar plasma pretreatment: 10 W, 10 min); ●, 10 min duration (Ar plasma pretreatment: 20 W, 10 min).

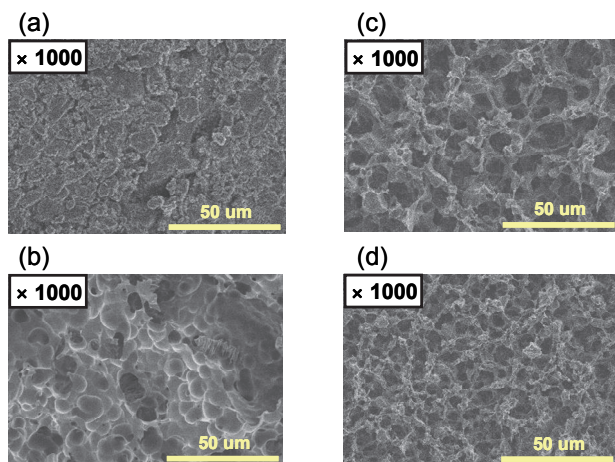


Fig. 5. SEM images of double-compressed tablets before and after plasma-irradiation for various duration.

Plasma conditions: O₂ 50 mL/min, 66.6 Pa.
 (a) blank; (b) 10 min duration (non-pretreatment);
 (c) 10 min duration (Ar plasma pretreatment: 10 W, 10 min); (d) 10 min duration (Ar plasma pre-treatment: 20 W, 10 min).

Fig 5(d). This should be attributed to the protective effect of the pre-crosslinked layer against the oxidative decomposition.

4. Conclusion

We have developed a sustained release drug delivery system by formation of a number of fine-micropores with pore sizes mostly ranging from 2 to 10 μm on the outer layer of two-layer tablet with plasma technique. The drug release profile from this system was confirmed in in vitro dissolution experiments. From the beginning of the dissolution test, a uniform release of drug was shown for more than 8 hours without spontaneous disintegration, and sustained release followed during 24-hours period. The results suggest that this system with plasma technique could be useful tool for the formulation strategy to obtain the desirable modulation of accurate drug release kinetics profile, according to its pharmacokinetics and therapeutic needs.

References

1. M. J. Gwen, R. R. Joseph, In G. S. Banker, C. T. Rhodes, Eds., *Modern Pharmaceutics*, 3rd Ed., Vol. 72, Marcel Dekker Inc. New York, 1996, 575.
2. Y. W. Chein, *Novel drug delivery systems*. 2nd ed., New York: Marcel Dekker Inc., 1997; pp.1-42.
3. M. Kuzuya, Y. Sasai, S. Kondo, Y. Yamauchi, *Curr. Drug Discov. Tech.*, **6** (2009) 135.
4. M. Kuzuya, Y. Sasai, Y. Yamauchi, S. Kondo, *Industrial Plasma Technology: Applications from Environmental to Energy Technologies*, WILEY- VCH Verlag GmbH & Co, in part, (2010) pp.113.
5. Y. Sasai, S. Kondo, Y. Yamauchi, M. Kuzuya, *Biomedical Engineering*, INTECH, (2011) pp101.
6. M. Kuzuya, A. Noguchi, H. Ito, M. Ishikawa, *Drug Delivery System*, **6** (1991) 119.
7. Y. Yamauchi, M. Kuzuya, Y. Sasai, S. Kondo, *J. Photopolym. Sci. Technol.*, **25** (2012) 535.
8. M. Kuzuya, Y. Yamauchi, J. Niwa, S. Kondo, Y. Sakai, *Chem. Pharm. Bull.*, **43** (1995) 2037.
9. M. Kuzuya, Y. Yamauchi, J. Niwa, S. Kondo, *Proc. SPSM*, **9** (1996) 55.
10. M. Kuzuya, Y. Sasai, S. Kondo, *J. Photopolym. Sci. Technol.*, **12** (1999) 75.