Construction of Matrix-type Drug Delivery System using Solid Phase Polymerization initiated by Plasma-induced Radicals

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1. Introduction

Plasma treatments are very effective in the modification of solid surfaces relating to cleaning, etching, activation, functionalization, and coating. Nowadays the techniques are becoming increasingly popular and developing for biomedical applications. [1, 2]

On the other hand, for the most suitable therapy, development of controlled-release systems for drug delivery is one of the most active areas today in the field of drug research. A wide variety of approaches of controlled-release DDS have been thus far investigated for oral application.

We have already reported that argon plasma-irradiated polyethylene containing plasma-induced surface radicals can undergo a radical-radical coupling reaction on its mechanical vibration [3, 4], and when the vibratory mixing was conducted in the presence of drug powder, the composite particle for sustained drug release was obtained. [5, 6]

On the basis of a series of such studies, we here report the surface modification of low-substituted hydroxypropyl cellulose (L-HPC) powder, which is one of the widely used pharmaceutical excipients, by mechanochemical reaction of N-vinylacetamide (NVA) and plasma-induced radicals of L-HPC. Furthermore, when mechanical vibration of NVA and plasma-irradiated L-HPC is similarly conducted with powdered drug, it can be expected that the drug is trapped among highly cross-linked powder particles resulted from mechanically-induced radical recombination. Thus, we present the preparation of composite powders for a sustained release DDS device induced by application of mechanical energy.

![Figure 1 Structures of L-HPC and NVA.](image)

2. Materials and Methods

Low-substituted hydroxypropyl cellulose (L-
HPC) powders of grade LH-21 were supplied by Shin-Etsu Chemical (Japan) and N-vinyl-acetamide (NVA) monomer by Showa Denko Co. (Japan) (Figure 1). Salicylamide was purchased from Wako Pure Chemical Industries, Ltd. (Japan). All dry powders were pulverized and screened with a 200-mesh sieve.

2.1 ESR Spectral Measurement

L-HPC (100 mg) was placed in a specially designed ampule (35 mm i.d., 120 mm long) connected with a capillary tube (2 mm i.d.) at the uppermost part of the ampule, and the ampule was filled with argon gas and sealed (13.3 Pa). Then the plasma state of argon was sustained during agitation of the samples by a radio frequency discharge of inductive coupling at 13.56 MHz with a supplied power (50 w). The ESR spectral measurements were performed while turning the ampule upside down at appropriate intervals. ESR spectra were recorded with a JES-FA200 spectrometer (JEOL) with X-band and 100 kHz field modulation. Care was taken to ensure that no saturation occurred and that the line shape was not distorted by excessive modulation amplitude. From a plot of the square root of the microwave power vs. the signal peak height, a microwave power level of 0.01 mW was chosen. The procedure is essentially the same as that reported earlier [3-6]. Schematic representation is shown in Figure 2.

2.2 Preparation of functionalized L-HPC Powders

Functionalized L-HPC powders were prepared as follows. A prescribed quantity of each plasma-irradiated powder was mechanically vibrated by vibratory milling apparatus (Shimadzu Co. Ltd.) equipped with a Teflon twin-shell blender (Figure 2). The Teflon twin-shell blender was used in the present study to eliminate any possibility of unnecessary side reactions such as mechanically-induced solid state singe electron transfer (SSET) reaction as in the case of using a metallic vessel [7-9].

2.3 Surface Characterization of the modified L-HPC powders

To confirm the chemical composition of the modified L-HPC powders, X-ray photoelectron spectrum (XPS) measurement was carried out using the conventional photoelectron spectroscopy apparatus, Shimadzu ESCA-3400. The Mg-Kα line (1253.6 eV), used as X-ray source, was incident at 45° with respect to the surface normal. The total energy resolution was approximately 0.5 eV. The base pressure in the photoelectron analysis chamber was maintained at least 5 × 10⁻⁶ Pa.

2.4 Dissolution Test

The discs prepared with the composite powders (10 mm diameter and 2 mm thickness) were cured by using compression moulding at 1 kN for 30 s. Then the drug release was evaluated in distilled water, according to the standard dissolution method using a rotational basket apparatus (Toyama Sangyo Co., Japan) at 37°C with 100 rpm. Released drug was periodically assayed by UV absorption spectrum at the wavelength of 300 nm.

3. Results and Discussion

3.1 Mechanochemical reactivity of plasma-induced L-HPC surface radicals

We have previously reported the ESR studies on elucidation of the surface radicals of argon plasma-irradiated L-HPC coupled with systematic computer simulations [10]. From the results, it has been disclosed that the plasma-irradiated L-HPC consists of four kinds of radicals, alkoxylalkyl radical at C1-C4, acylalkyl radical at C2-C3, acylalkyl radical at the isopropyl side chain and dangling bond sites (DBS).
Figure 3 (a) and (b) show the ESR spectra of 120 s plasma-irradiated L-HPC powders and the mechanical-vibrated sample after plasma-irradiation, respectively. In comparison with both spectra, although the spectral patterns did not change by vibratory mixing, the ESR intensity decreased. Likewise, when the vibratory mixing is conducted in the presence of solid-state vinyl monomer, NVA, the intensity of the lateral peaks increased (shown with arrows in Figure 3 (c)) in the resultant spectrum as compared with that of the L-HPC.

Figure 3  ESR spectra of (a) plasma-irradiated L-HPC powder, (b) L-HPC fractured for 5 min after plasma treatment, (c) fractured with NVA for 5 min. (d) The remaining line (broken line) in the observed ESR spectrum (solid line, (c)) after subtraction of the L-HPC radicals (dotted line).

In order to identify the radicals which generate during the vibrating process, the technique of spectral subtraction was used. As shown in Figure 3 (d), the residual spectrum (broken line) was obtained as a triplet by subtraction of a spectrum of L-HPC radicals (dotted line) from the observed spectrum (solid line) of L-HPC vibrated with NVA. We note that the residual spectral feature is very similar to that observed by mechanical fracture of poly-NVA, being assigned to an end-chain radical (data not shown). This result indicates that L-HPC radicals initiated radical polymerization of NVA resulting in the formation of L-HPC-block-NVA on the L-HPC surface.

3.2 Surface Analysis of the L-HPC powders grafted NVA polymer

XPS has been employed to assess the chemical changes that occur on the L-HPC powder surface. The L-HPC vibrated with NVA under anaerobic condition at room temperature was washed with distilled water to eliminate unreacted NVA. The resultant residue sample was then dried in vacuum at 348 K for 24 h. Figure 4 shows the XPS survey scan (0–1000 eV) and N1s core-level spectra of L-HPC powders with or without functionalizing treatment.

For treated with NVA, new peaks appeared about 401 eV showing the presence of nitrogen containing groups on the surface of L-HPC, indicating that poly-NVA chains grafted on L-HPC powders. Moreover, XPS spectra show a increase of grafted polymer by increasing the treatment time, assessed by an appreciable decrease of all the bands related to L-HPC.

Figure 4  XPS survey scan spectra (0–1100 eV) and N1s core-level spectra of (a) pristine L-HPC powder, (b) plasma-irradiated L-HPC fractured with NVA for 5 min and (c) fractured for 30 min. The spectra are offset for clarity.
3.2 Dissolution properties of salicylamide

The drug-release test of tablets prepared with composite particles was conducted.

The drug release profiles are shown in Figure 5. The salicylamide release from the tablets prepared as described above was significantly sustained, although the blendmer of virgin L-HPC, NVA and salicylamide powder has shown no sustainable release. It was indicated that drug powders trapped in small pores of the intricate cross-linked polymer matrix were eluted gradually. The results also showed the effect of NVA amount in preparation of compressed tablet on the dissolution of salicylamide.

![Figure 5](image)

Figure 5 Effect of NVA content on salicylamide release profiles from the tablets prepared with powder sample composed of NVA and plasma-induced radical-containing L-HPC. Plasma conditions: 50 w; 13.3 Pa. Mechanical conditions: 30 min; 60 Hz; anaerobic condition.

However, it is seen that the drug release rates change to be higher as the mixed content of NVA increases to more than 15%, being ascribed to enlargement of the matrix size of polymer networks.

4. Conclusions

In this study, we aimed to construct the high functional surface of L-HPC powder by vibratory mixing of reactive surface radicals formed with plasma treatment and solid-state vinyl monomer.

From the results of ESR and XPS analysis, the L-HPC-block-poly-NVA was synthesized successfully on the L-HPC surface by radical polymerization of NVA, which was initiated by the plasma-irradiated radicals located on the surface. Drug release properties from tablets prepared with or without NVA grafted L-HPC have been studied and compared for the different contents of NVA. The results showed a remarkable improvement in comparison with original non-surface modified L-HPC powder.

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