Novel and Simple Preparation Method of Matrix-Type Composite Particles for Controlled Drug Release by Mechanical Action

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Matrix-type composite particle for controlled drug release can readily be prepared through a totally dry process by simple anaerobic mechanical vibration of mechanoradical-containing ethylcellulose (EC) with theophylline powder due to occurrence of collision-induced radical–radical coupling reaction to form interparticle matrices, as well as the formation of interparticle network when solid-state vinyl monomer was further added.

Key words matrix-type composite particle; controlled release; vibratory milling; mechanoradical; radical coupling; electron spin resonance (ESR)

Recently we have reported the mechanically-induced radical (mechanoradical) formation of several glucose-based polysaccharides such as anomeric cellulose and amylose,[1] and pharmaceutically important substituted-celluloses[2] under anaerobic conditions, coupled with the concomitant changes in physicochemical properties, and it was found that the mechanoradicals generated in substituted-celluloses have a greater tendency to dissipate after reaching the maximum value in spin concentration during the course of mechanical vibration. This result has been ascribed to the occurrence of intra- and inter-segmental radical–radical coupling reactions including those in an interparticle fashion. We have also demonstrated that argon plasma-irradiated polyethylene, high density (HDPE) and low density (LDPE), containing plasma-induced surface radical 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 (theophylline), the composite particle for sustained drug release was obtained.[5]

On the basis of a series of such studies, one may expect that the matrix-type DDS can be prepared without plasma-irradiation, when the vibratory mixing is conducted using mechanoradical-containing polymers in the presence of drug powder.

In fact, we were able to obtain such composite particles applicable to matrix-type DDS by simple vibratory mixing of mechanoradical-containing ethylcellulose (EC) powder, which is one of the widely used pharmaceutical excipients, in the presence of theophylline powder as a model drug, so as to immobilize it into EC matrix.

A prescribed quantity of EC was ground with a vibratory ball milling apparatus (Shimadzu Corp.) equipped with a stainless-steel ball (6 mmϕ) in a stainless-steel twin-shell blender (7.8 mmϕ, 24 mm long) at 60 Hz under anaerobic conditions (nitrogen environment, oxygen concentration $<$0.01 ppm) in a vacuum glovebox at room temperature to generate the mechanoradicals of EC. The reaction was monitored by electron spin resonance (ESR) and showed the maximum value in spin concentration (*ca.* 1.6×10^{17}/g) on the vibratory milling for 15 min. Then, the vibratory mixing of EC powder (100 mg) thus treated for 15 min was carried out with theophylline powder (10 mg) using the same vibratory ball milling apparatus, but equipped with specially made Teflon ball (6 mmϕ) in Teflon twin-shell blender (7.8 mmϕ, 24 mm long) at 60 Hz for 4 h under which no mechanoradical is newly formed.

Likewise, when the above-mentioned vibratory mixing is conducted in the presence of solid state vinyl monomer, the mechanically-induced solid state polymerization would concomitantly proceed, which would eventually result in the formation of interparticle network, at least, partially, the vinyl monomer acting as a size controller of the polymer network in the matrices.

With this thought in mind, vibratory mixing of powders composed of mechanoradical-containing EC and methacryloyl acetaminophen (*p*-methacryloyloxy acetanilide) (MA)[6] (totally 100 mg) was similarly conducted in the presence of theophylline (10 mg) using the same vibratory ball milling apparatus. The ESR spectra of the reaction mixture has shown the rapid conversion of EC radical into the end-chain alkyl radical of MA identical with those of all kinds of mechanically-fractured methacrylic polymers,[7] confirming that mechanically-induced solid state polymerization of MA has been initiated from EC mechanoradical. And, the reaction has completed in conducting the vibratory mixing for 4 h, evidenced by observing the disappearance and appearance of vinyl proton signals of MA monomer and the corresponding alkyl proton signals of the polymer in the ^{1}H-NMR spectra by FT-NMR spectrometer (JNM-GX270, JEOL). Figure 1 shows the scanning electron microphotograph of the spherically-shaped composite particle thus obtained.

The drug-release test of composite particles (5.0 mg) was conducted in 20 ml of pH 7.4 phosphate buffer solution at 37.0$\pm$0.2 °C in a heterogeneous system. The test solution dispersed composite particles was shaken at 80 strokes/min. Released theophylline was periodically assayed by UV absorption spectrometer (UV-2200, Shimadzu Corp.) at the wavelength of 270 nm, and the drug release profiles are shown in Fig. 2. In fact, the theophylline release from the composite particle prepared as described above was significantly sustained, although the blendmer of virgin EC and theophylline powder has shown no sustainable release (not

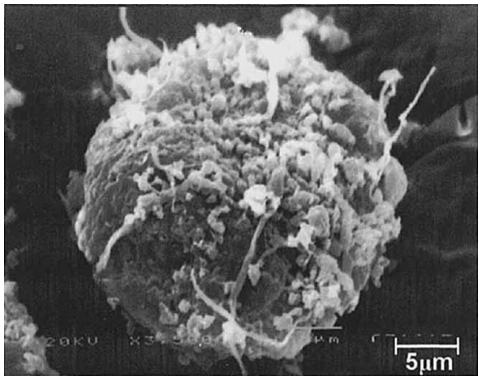

Fig. 1. Scanning Electron Microphotograph of Composite Particle Prepared by Vibratory Mixing of Mechanoradical-Containing EC (50 mg), MA (50 mg) and Theophylline Powder (10 mg)

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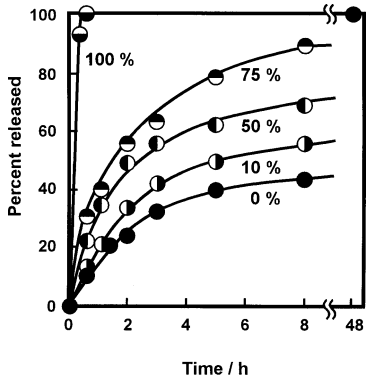

Fig. 2. Theophylline Dissolution Profiles from the Composite Particles (5 mg) Prepared by Vibratory Mixing of Powders (100 mg) Composed of Mechanoradical-Containing EC and MA with Theophylline (10 mg) under Anaerobic Condition

The percentage values shown in figure denote the mixing ratio of MA to EC in composite particles.

shown in Figure). It is seen that the drug release rates change to be higher as the mixed content of hydrophobic MA increases, being ascribed to enlargement of the matrix size of polymer networks.

It was also found that the drug release rate constant deduced from Baker–Lonsdale model[8] has shown to be a good linear relationship with the mixed content of MA. The result indicates that the composite particles thus prepared were suitable for the sustained drug release from a spherical matrix-type dosage form. Thus, it can be concluded that the controlled drug release from the present composite particles can be achieved by controlling the ratio in quantity between EC and vinyl monomer.

The result reported herein will spark new interest in one of the research areas of molecular pharmaceutics, and we are now actively elaborating this initial study. It is hoped that a wide variety of applications will be gained in the course of attempt now in progress, including an effort to deliver a higher drug-payload.

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