# Mechanochemical Solid-State Polymerization (XI): Effect of Water-Insoluble Pharmaceutical Aids on Drug Release from Mechanically Synthesized Polymeric Prodrugs

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**We discuss here the effect of water-insoluble pharmaceutical aids on the nature of drug release from composite polymeric prodrugs synthesized by mechanochemical solid-state polymerization. Magnesium stearate (Mgst) and hydrogen castor oil (HCO) were used as water-insoluble pharmaceutical aids. Composite polymeric prodrugs were synthesized by the mechanochemical solid-state polymerization of a vinyl monomer of 5-fluorouracil (I) in the presence of Mgst or HCO. The molecular weight of the resulting polymeric prodrugs increased with increasing the content of Mgst or HCO. Prodrug hydrolysis was carried out in a heterogeneous system in phosphate buffer at pH 6.8 and 37 °C. The rate of drug release from the composite polymeric prodrug containing Mgst (Poly-Mgst) was faster than that from polymeric prodrug containing no pharmaceutical aids (Poly-Non), while hydrolysis of the composite polymeric prodrug containing HCO (Poly-HCO) was slower than Poly-Non. Scanning electron microscope (SEM) photos showed the surface of Poly-HCO was smoother than that of Poly-Non and Poly-Mgst. It was suggested that the slower drug release from Poly-HCO may be responsible for the smaller specific surface area than that of Poly-Non. It was also shown that the rate of drug release from the composite polymeric prodrugs decreases with increasing the content of Mgst or HCO. Hence, novel composite polymeric prodrugs with a variety of drug release rates can be prepared by mechanochemical solid-state polymerization in a totally dry process.**

**Key words** polymeric prodrug; mechanochemical polymerization; drug release; magnesium stearate; hydrogen castor oil

Polymeric prodrugs, in which a drug is covalently attached to a polymeric backbone, possess unique properties, distinct from those of the corresponding lower molecular weight drugs. The polymeric prodrugs present several possible pharmaceutical advantages: (1) increased absorption, leading to improved drug bioavailabilty, and (2) various properties (*e.g.* sustained- and controlled-release, targeting) that could be incorporated into a polymeric prodrug, hence the rate of drug release and its distribution in the body could be controlled.[1,2]

We have previously reported the convenient synthesis of novel polymeric prodrugs by mechanochemical polymerization and the nature of their drug release in heterogeneous systems.[3—17] The monomers, prepared on the basis of the structural criteria derived from quantum chemical considerations undergo facile mechanochemical solid-state polymerizations to give the corresponding polymeric prodrugs in essentially quantitative yield, thus, eliminating the need for any work up of reaction mixture.[4,7] One of the most striking properties of the polymers produced by this method is that the resulting polymeric prodrugs are of very low heterogeneity (*i.e.* they have a very narrow molecular weight distribution), which is of great value for highly functionalized polymeric prodrugs. Therefore, the present reaction seems potentially applicable to a wide variety of vinyl monomer derivatives of bioactive compounds, possessing different physicochemical properties, and provides a novel and simple methodology for the synthesis of polymeric prodrugs.

We have previously reported the preparation of polymeric prodrugs in which fine particles of the water-soluble pharmaceutical aid, lactose, are dispersed during synthesis (Fig. 1A).[11] The kinetics of drug release from these composite polymeric prodrugs was studied, and compared with that of the blendmer, which was prepared by physical mixing of the polymeric prodrugs with lactose (Fig. 1B). The rate of drug release from the composite polymeric prodrugs was faster than that of the blendmer and increased with increasing content of lactose, up to 75% (w/w). Preparation of such a composite polymeric prodrugs by solution polymerization would be difficult.

In this paper we aimed to control drug release from composite polymeric prodrugs containing water-insoluble pharmaceutical aids. Magnesium stearate (Mgst) and hydrogen castor oil (HCO) were selected due to representative water-insoluble pharmaceutical aids and added using the same method as for the preparation of lactose composites, and their effect on the physicochemical properties of the resulting composite prodrugs was studied. The homopolymer of a vinyl derivative of 5-fluorouracil was used as a model polymeric prodrug. The hydrolysis of the powdered prodrugs was performed in a heterogeneous system (suspended solution) and the effect of water-insoluble pharmaceutical aids on drug release was discussed.

## Experimental

**Materials** 1-(2-Methacryloyloxy)ethylcarbamoyl-5-fluorouracil (I) was prepared according to the literature.[8] Magnesium stearate (Mgst) and hydrogen castor oil (HCO) were purchased from NOF Corp. and Kawaken Fine Chemicals Co., Ltd., respectively.

**Mechanochemical Solid-State Polymerization** A mixture (100 mg) of I and Mgst or HCO, in various ratios (0—5% (w/w) for Mgst, 0—10% (w/w) for HCO), was mechanochemically fractured by ball milling in a stainless steel twin-shell blender at room temperature for 2 h in a vacuum glove box (Sanplatec Corp.) according to the method previously reported.[11] Air in the vacuum glove box was replaced with purified nitrogen gas. Any remaining oxygen in this system was removed with a Model 1000 Oxygen Trap (GL Sciences Inc.). The oxygen concentration was monitored with an oxygen analyzer (LC750/PC-120, Toray Engineering Co., Ltd.) and kept below 20 ppm.

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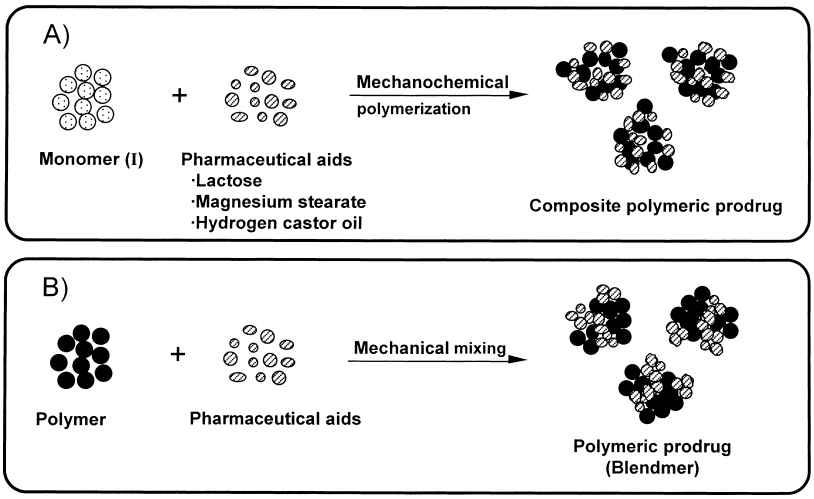



Fig. 1. Conceptional Illustration for the Synthesis of A) Composite Polymeric Prodrug by Mechanochemical Solid-State Polymerization in the Presence of Pharmaceutical Aids and B) Polymeric Prodrug Blendmer by Sequential Preparation of Polymeric Prodrug Followed by Mechanical Mixing with Pharmaceutical Aids

**Proton Nuclear Magnetic Resonance ($^1$H-NMR) Spectral Measurement** $^1$H-NMR spectra were recorded on a JEOL JNM-GX270 FT-NMR spectrometer in dimethylsulfoxide-$d_6$ (DMSO-$d_6$). The $^1$H-NMR spectra of each of the fractured mixtures were taken after being exposed to air to quench any radicals.

**Method of Hydrolysis** The hydrolysis of powdered polymeric prodrugs (5.0—6.0 mg) was conducted in pH 6.8 phosphate buffer at 37±0.2 °C, in a heterogeneous system using a flow-through-cell apparatus, as previously reported.[11] Released 5-fluorouracil (5-FU) was periodically assayed by UV absorption (Recording Spectrophotometer UV-2200 (P/N 206-17000), Shimadzu Co.) at 266 nm. Total amount of released 5-FU assayed by UV absorption was equal to the amount of 5-FU bounded to the polymeric prodrug, which was calculated from the weight and mixing ration of the composite polymeric prodrug used.

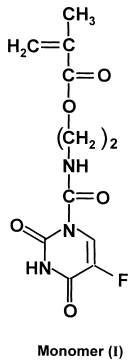
**Particle Diameter Measurement** The particle size of polymeric prodrugs was measured *via* light scattering (LS100Q, Coulter Co.), using diode laser light of wavelength 750 nm, equipped with a small volume module (SVM, Coulter, Co.) in a methanol suspension. Data was collected and averaged over 60 s. Data analysis was performed using the Coulter LS control program (Coulter Co.) with a 32-bit microcomputer (NEC VALUESTAR NX).

**Molecular Weight Measurement** The molecular weight measurements were taken with a gel permeation chromatograph (GPC, Shimadzu, LC-6A), equipped with a refractive index detector (Shimadzu, RID-6A), gel column (Shodex, KD-800P and KD-80M) and data analyzer (Shimadzu, Chromatopac CR-4A) under the following conditions: elution solvent, dimethylformamide (DMF) containing 0.01 M LiBr; flow rate, 0.7 ml/min; column temperature, 40 °C. Calibration was carried out with a polyethylene oxide standard.

**Scanning Electron Microscope (SEM)** The microscopic changes in the surface morphology of the powdered polymeric prodrug were photographed by SEM (JEOL, JSMT-330A) with accelerating voltage of 15 kV and magnification of ×5000 and ×7500.

## Results and Discussion

**Physicochemical Properties of Polymeric Prodrugs Containing Water-Insoluble Pharmaceutical Aids** The methacryloyl derivative of 5-FU (I) was chosen as a model monomer of a bioactive compound (Chart 1). The mechanochemical polymerization of I in the presence of the water-insoluble pharmaceutical aids, magnesium stearate (Mgst) or hydrogen castor oil (HCO), in various ratios (0—5% (w/w) for Mgst, 0—10% (w/w) for HCO), was carried out for 2 h to obtain the composite polymeric prodrugs. The polymer conversion of each fractured mixture was determined by $^1$H-NMR, as previously reported,[11] following the disappearance




Monomer (I)

Chart 1

of vinyl protons and the appearance of the corresponding alkyl protons of the polymer. It was confirmed that polymerization of each mixture proceeded to completion. Physicochemical properties of these composite polymeric prodrugs are shown in Table 1. Poly-Non, Poly-Mgst and Poly-HCO denote the polymeric prodrug without water-insoluble pharmaceutical aids, with Mgst and with HCO, respectively. The value in parentheses denotes the percent by weight of pharmaceutical aids in the composite polymeric prodrugs. Although the mechanochemical polymerization of I containing Mgst or HCO was carried out for 3 h, the number average molecular weight values indicated that the reaction was complete after 2 h.

The weight average particle diameter of Poly-Mgst and Poly-HCO ranged from 33 to 43 $\mu$m, and was smaller than that of Poly-Non (83 $\mu$m). The number average molecular weight of the composite polymers increased with increasing content of Mgst or HCO. We note that the molecular weight of the polymers synthesized by mechanochemical polymerization increases with decreasing mechanical energy, which suggests that Mgst and HCO are acting as buffers and that the mechanical action is weakened by their presence. This phenomenon is opposite to that of mechanochemical polymerization in the presence of lactose, in which the molecular weight of the resulting polymer decreases with increasing

Table 1. Physicochemical Properties of Poly-Non, Poly-Mgst and Poly-HCO

| Polymeric prodrug | Content (%) | Particle diameter ($\mu$m) | Number average molecular weight ($\bar{M}n$) | Heterogeneity ($\bar{M}w/\bar{M}n$) |
|---|---|---|---|---|
| Poly-Non | 0.0 | 82.8 | 32000 | 1.11 |
| Poly-Mgst(2) | 2.0 | 42.8 | 45000 | 1.12 |
| Poly-Mgst(5) | 5.0 | 37.5 | 47000 | 1.15 |
| Poly-HCO(2) | 2.0 | 37.0 | 44000 | 1.13 |
| Poly-HCO(5) | 5.0 | 34.4 | 46000 | 1.13 |
| Poly-HCO(10) | 10.0 | 32.8 | 50000 | 1.15 |

$\bar{M}w$; weight average molecular weight.

content of lactose.[11] It is of interest that all polymeric prodrugs showed lower heterogeneity (*i.e.* they have narrow molecular weight distributions).

**Drug Release from Polymeric Prodrugs Containing Water-Insoluble Pharmaceutical Aids** The hydrolysis of composite polymeric prodrugs was conducted in pH 6.8 phosphate buffer at 37±0.2 °C in a heterogeneous system with a flow-through-cell apparatus. Released 5-FU was periodically assayed by UV absorption at 266 nm. The results are shown in Fig. 2. It was separately confirmed that all composite polymeric prodrugs released 5-FU quantitatively.

It should be noted that, although we do not show the profile of drug release from the higher molecular weight Poly-Non ($\bar{M}w=50000$), its release profile was similar to that of Poly-Non ($\bar{M}w=32000$), indicating that drug release is unaffected by polymer molecular weight, within this range. The rate of drug release from Poly-Mgst was faster than that from Poly-Non, which was faster than from Poly-HCO. For both Poly-Mgst and Poly-HCO the rate of drug release was slower with increasing content of the Mgst and HCO. As the particle diameter of Poly-Mgst was smaller than that of Poly-Non (Table 1), the specific surface area of Poly-Mgst must be larger than that of Poly-Non. We conclude that the drug release from Poly-Mgst proceeds faster than that of Poly-Non due to the increase in specific surface area. Conversely, the particle diameter of Poly-HCO was slightly smaller than that of Poly-Mgst, (while their molecular weights are similar—see Table 1), but Poly-HCO hydrolysis was slower than that of Poly-Mgst. The HLB (hydrophile-lipophile balance) values of Mgst and HCO, as calculated by the equation proposed by Oda *et al.*,[18] were ≧9.1 and 4.4, respectively, indicating that HCO is more hydrophobic than Mgst, which may explain why drug release from Poly-HCO is slower than from Poly-Mgst. The surface morphology of the polymers may also affect the rate of drug release. The surface characteristics of the composite polymers were examined by scanning electron microscopy (SEM). Figure 3 shows several SEM photographs of the surface of Poly-Non, Poly-Mgst(5) and Poly-HCO(5).

The surface morphologies of Poly-Non and Poly-Mgst(5) are similar to each other and show a very rough texture, differing from the surface of Poly-HCO(5) which appears much smoother. The melting points of the Mgst and HCO used were 132 °C and 82 °C, respectively. During the mechanochemical polymerization, the temperature of the metallic reaction vessel increased to 40 °C, induced by mechanical action. Hence the lower melting HCO particles may have been softened by the local heat, inducing a surface morphology change. It may be one of the reasons why Poly-HCO has a lower specific surface area.

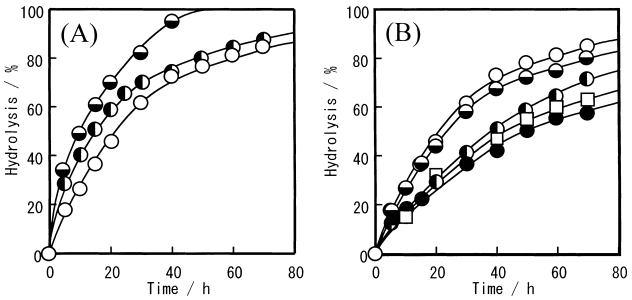



Fig. 2. Hydrolysis Profiles of Polymeric Prodrug Powder of I Containing Water-Insoluble Pharmaceutical Aids Prepared by Mechanochemical Polymerization

(A) Magnesium stearate, (B) hydrogen castor oil. ○, polymeric prodrug without pharmaceutical aids; ◒, 2% pharmaceutical aids; ◐, 5% pharmaceutical aids; ●, 10% pharmaceutical aids; □, blendmer (10% HCO).

Moreover, the blendmer (Blend-HCO(10)) containing 10% (w/w) HCO was prepared by physical mixing of Poly-Non and HCO. The rate of drug release from Blend-HCO(10) was faster than that from Poly-HCO(10). The water-insoluble pharmaceutical aids in composite polymer particle can retard the influx of water into the particle and the diffusion of the hydrolyzed drug from the particle. Hence it is considered that fine particles of HCO may be more homogeneously dispersed in Poly-HCO(10) particle than in Blend-HCO(10) particle. The same explanation can be applied to the composite polymeric prodrug containing lactose.[11]

**Kinetic Analysis of Drug Release** The rate of drug release from a water-insoluble polymeric prodrug in a heterogeneous system frequently obeys the apparent first-order kinetics. The apparent first-order rate constant contains several parameters, such as rate constant of hydrolysis, diffusion coefficient and so on. Therefore, it is difficult to reveal significant factors of drug release from the apparent first-order rate constant. In the previous paper,[12] we theoretically derived the rate equation of drug release from water-insoluble polymeric prodrugs in a heterogeneous system based on a simple model, and revealed that this equation is useful to analyze drug release from these polymeric prodrugs. Thus, kinetic analysis of drug release was carried out using this equation (Eq. 1).

$$Mt/M_\infty = 3at - 3a^2(1+b/2)t^2 + a^3(1+4b)t^3 - (7/2)a^4bt^4 - a^5bt^5 \quad (1)$$

$$a = k/\rho r_0, \quad b = r_0 k/D\rho$$

where $Mt$ and $M_\infty$ are the amount of drug released at time

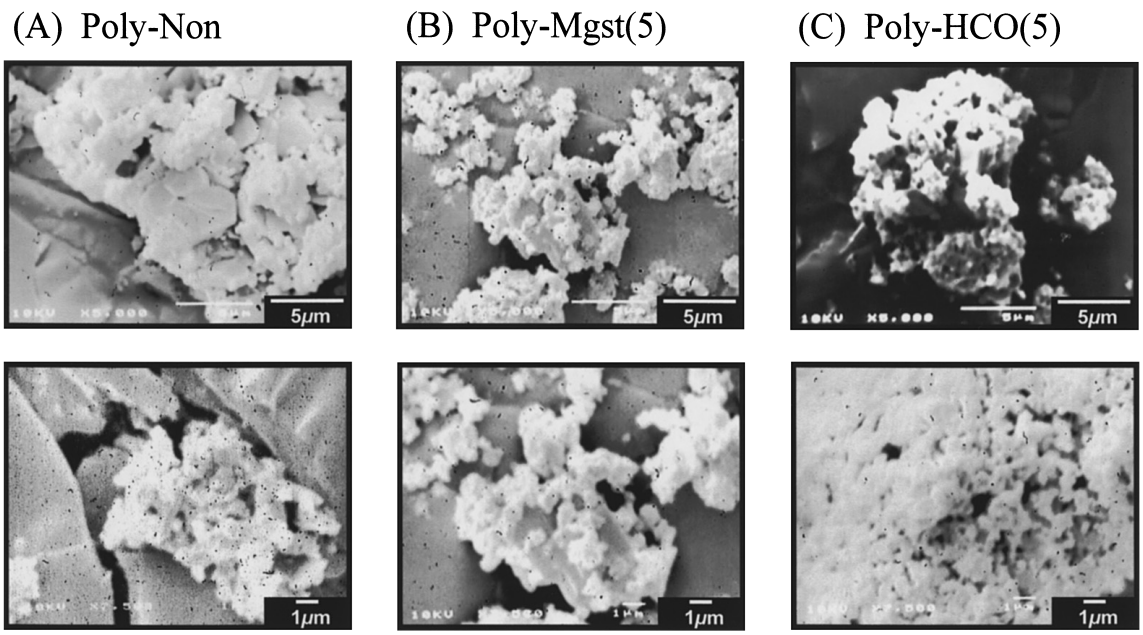



Fig. 3. SEM Photographs of the Surface of Poly-Non, Poly-Mgst(5) and Poly-HCO(5)

Table 2. Rate Constant of Hydrolysis ($k$) and Diffusion Coefficient ($D$) of Composite Polymeric Prodrugs of I Prepared by Mechanochemical Polymerization

| Polymeric prodrug | $k\times10^{-4}$ | $D\times10^{-12}$ | Correlation coefficient |
|---|---|---|---|
| Poly-Non | 19.9 | 17.2 | 0.9982 |
| Poly-Mgst(2) | 18.5 | 13.2 | 0.9598 |
| Poly-Mgst(5) | 14.5 | 7.27 | 0.9706 |
| Poly-HCO(2) | 7.44 | 5.35 | 0.9809 |
| Poly-HCO(5) | 4.38 | 2.48 | 0.9952 |
| Poly-HCO(10) | 3.43 | 2.24 | 0.9632 |

$t$ and the total amount of drug in the composite polymeric prodrug, respectively. $k$, $D$, $r_0$ and $\rho$ denote rate constant of hydrolysis (mol/m$^2$/h), diffusion coefficient (m$^2$/h), initial radius of polymeric prodrug powders (m) and amount of drug contained in powdered polymeric prodrug per unit volume (mol/m$^3$), respectively. The progressive changes in drug release were obtained from this equation by iteratively fitting the parameters ($a$ and $b$) with the ratio of released 5-FU, using the nonlinear least squares method. The particle density was determined by the pycnometer method. The particle density was 1.26 g/cm$^3$ (4420 mol/m$^3$) for each sample.

Table 2 shows the rate constant of hydrolysis ($k$) and the diffusion coefficient ($D$) calculated from Eq. 1. The values of $k$ and $D$ for Poly-Mgst(2) and Poly-Mgst(5) were smaller than those for Poly-Non. It was observed that $k$ and $D$ were smaller with increasing content of Mgst. The rate of hydrolysis in heterogeneous systems is directly related to the surface area of the particles. *i.e.* a smaller surface area will result in a slower hydrolysis. Increasing the content of Mgst results in a decrease in the amount of prodrug per unit surface area of the polymer, which would cause a decrease in the rate of hydrolysis, consistent with our observations. Conversely, when using composite polymeric prodrug with water-soluble lactose in a heterogeneous system, the lactose will dissolve in water, resulting in an increased surface area and a faster hydrolysis.[11] It would be expected that the diffusion coefficient would decrease with increasing content of Mgst. The changes in $k$ and $D$ for Poly-HCO when varying their concentration were similar to those for Poly-Mgst. However, the values of $k$ and $D$ for Poly-HCO were smaller than those for Poly-Mgst when present at the same concentration, which could be explained by the difference of their surface morphologies.

## Conclusion

The conclusions drawn from the present study can be summarized as follows. The mechanochemical polymerization of I in the presence of the water-insoluble pharmaceutical aids, magnesium stearate (Mgst) or hydrogen castor oil (HCO), in various ratios was carried out for 2 h to obtain the composite polymeric prodrugs. The molecular weight of the resulting composite polymeric prodrugs increased with increasing the content of Mgst or HCO, suggesting that they act as a buffer during the reaction and that the mechanical action was weakened by their addition. The hydrolysis of composite polymeric prodrugs was conducted in pH 6.8 phosphate buffer at 37±0.2 °C in a heterogeneous system. The rate of drug release from Poly-Mgst was faster than that from Poly-Non, resulting from the smaller particle diameter of Poly-Mgst over that of Poly-Non. On the other hand, the rate of drug release from Poly-HCO was slower than from Poly-Mgst and Poly-Non. It was suggested that the hydrophobicity of HCO and the surface morphology of Poly-HCO resulted in the slower release.

It was revealed by kinetic analysis of drug release that the rate constant of hydrolysis and the diffusion coefficient for composite polymeric prodrugs tended to decrease with increasing the content of hydrophobic pharmaceutical aids. The decrease in rate constant of hydrolysis with increasing content of Mgst could be attributed to the decrease in content of polymeric prodrugs per unit surface area. It was also suggested that the variation in surface morphologies was one of

the reasons for the differences in rate constant of hydrolysis and diffusion coefficient between Poly-Mgst and Poly-HCO.

In summary, this technique seems applicable to a wide variety of compounds. Careful selection, based on physicochemical properties, of pharmaceutical aids to be incorporated into novel composite polymers, will result in prodrugs with a variety of drug release rates that can be synthesized by mechanochemical solid-state polymerization.

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