# Controlled Release of Drug via Methylcellulose-Carboxyvinylpolymer Interpolymer Complex Solid Dispersion

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## ABSTRACT

The purpose of this research was to examine the controlled release of phenacetin (PHE) from solid dispersion by the formation of an interpolymer complex between methylcellulose (MC) and carboxyvinylpolymer (CP). The PHE/polymer composition ratio was fixed at 20:80 (w/w) in the solid dispersion. The effect of the MC/CP ratio and molecular weight of MC on the PHE release was studied. The release of PHE from the solid-dispersion granules depended on the MC/CP ratio, with a ratio of 50:50 giving the lowest rate of release. In aqueous solution, this MC/CP ratio resulted in the lowest transmittance, suggesting a maximal extent of interpolymer complex formation between MC and CP. Furthermore, at a MC/CP ratio of 50:50, the release of PHE from the solid dispersion granules decreased as the molecular weight of the MC increased, reaching a plateau at molecular weights $\geq$180,000. The contributions of diffusion and polymer relaxation to PHE release increased as the molecular weight of the MC increased. This study shows that it is feasible to control the release of PHE from MC-CP solid dispersion granules by modulating complex formation between MC and CP, which can be accomplished by altering the MC/CP ratio and the molecular weight of MC.

**KEYWORDS:** controlled release, solid dispersion, polymer complex, methylcellulose, carboxyvinylpolymer

## INTRODUCTION

Solid dispersion, in which compounds are dispersed into water-soluble carriers, has been generally used to improve the dissolution properties and the bioavailability of drugs that are poorly soluble in water.[1-5] Phosphatidylcholine and lactose have been tested as carriers,[6,7] and the twin-screw extruder method has been studied as a new technique for solid dispersion.[8]

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Solid dispersion has also been applied for the controlled release of drugs. Previous reports have shown that by using solid dispersions containing a polymer blend, such as hydroxypropylcellulose and ethylcellulose, it is possible to precisely control the rate of release of an extremely water-soluble drug, such as oxprenolol hydrochloride.[9-13] In this case, the water-soluble hydroxypropylcellulose swells in water and is trapped in the water-insoluble ethylcellulose so that the release of the drug is slowed. These studies have shown that there is a linear relationship between the rate of release of the water-insoluble drug and its interaction with the polymer.[14-16]

Two polymer carriers used for solid dispersion, poly(ethylene oxide) (PEO), which has an ether group in its structure because of repeats of $-CH_2-CH_2-O-$, and carboxyvinylpolymer (Carbopol [CP]), which is a kind of poly(carboxylic acid), have been found to interact.[17] Attempts have been made to control an antipyretic phenacetin (PHE) release from the solid dispersion by adjusting the hydrogen bonding between the ether group of PEO and the hydroxyl of carboxyl groups of CP.[18-20] Methylcellulose (MC) is water-soluble polymer that is widely used in the pharmaceutical field. MC has the hydroxyl group in a structure and is interactive with the carboxylic acid of CP, as well as PEO.

The purpose of this research was to examine the controlled release of PHE from solid dispersion by the formation of an interpolymer complex between MC and CP using 6 different molecular weights of MC. The effect of the MC/CP ratio and molecular weight of MC on the PHE release was studied. The results of these studies also allowed us to clarify the mechanism of drug release from the granules.

## MATERIALS AND METHODS

### *Materials*

The antipyretic PHE (Tsukishima Pharmaceutical Co, Ltd, Tokyo, Japan) was used as the model drug. The molecular weight and density of PHE are 179 and 1.21 g/cm$^3$, respectively. Six grades of MC (MC15, MC25, MC100, MC400, MC4000, and MC8000) were generously provided by Shin-Etsu Chemical Co, Ltd (Tokyo, Japan). CP (Carbopol 934P, Noveon Inc, Brecksville, OH) was generously provided by CBC Co, Ltd (Tokyo, Japan). The average

molecular weights and densities of MC15, MC25, MC100, MC400, MC4000, and MC8000 were 70,000, 83,000, 118,000, 180,000, 330,000, and 440,000 and 1.33, 1.35, 1.40, 1.42, 1.43, 1.36 g/cm$^3$, respectively, and CP had a nominal average molecular weight of 3,000,000 and a density of 1.41 g/cm$^3$. The densities were calculated from the volume measured with an Air Comparison Pycnometer (model 930, Toshiba-Beckman, Tokyo, Japan).

### *Methods*

#### *Preparation of Solid Dispersions*

PHE and MC were dissolved together, and CP was dispersed in 1:1 (v/v) water/ethanol. The PHE-MC solution and the CP dispersion were mixed for 24 hours, after which solvent was removed from both by evaporation with an evaporator at 50°C.[19,20] The solid dispersions were then ground with a cutter-type mill (Philips, Tokyo, Japan) and dried at 50°C for 24 hours under reduced pressure. The granules obtained were passed through an 850-μm-diameter to 1,000-μm-diameter sieve. The PHE/polymer composition ratio was fixed at 20:80 (w/w) in the solid dispersion, whereas the MC/CP ratios were varied and included 100:0, 90:10, 70:30, 50:50, 30:70, 10:90, and 0:100 (w/w).

#### *Physicochemical Properties of Solid Dispersions*

Powder radiograph diffraction patterns were generated with a RAD-IB diffractometer (Geigerflex, Rigaku, Tokyo, Japan). The operating conditions were as follows: target, Cu; filter, Ni; voltage, 40 kV; current, 20 mA, and scanning speed, 2θ = 4°/min. Differential scanning calorimetry (DSC) curves were measured with a Thermo Plus 2 DSC instrument (DSC8230, Rigaku). The heating rate was 4°C/min, and the nitrogen gas flow rate was 70 mL/min. Physical mixture of PHE/MC100/CP was prepared by mixing the powders of PHE, MC100, and CP in a test tube using a vortex mixer.

#### *Drug Release Studies*

The sieves with their openings at 63, 75, 150, and 180 μm were used. One gram of PHE was put on the 180-μm sieve, and the sieves were vibrated with a Sieve Vibrator (Tsutsui Rikagaku Kikai, Tokyo, Japan). PHE (75-μm to 150-μm sieve) was used for the dissolution test. The drug release study was performed according to the Japanese Pharmacopeia 14$^{th}$ ed. using a NTR-6100A dissolution tester (Toyama Sangyo, Osaka, Japan). The solid dispersion granules, which contained 6 mg of PHE, were used. The conditions were as follows: test solution, 900 mL of distilled water; temperature, 37 ± 0.5°C; and paddle rotation, 100 rpm. The quantity of PHE was determined by measuring the absorbance at 243 nm with a UV-1200 spectrophotometer (Shimadzu, Tokyo, Japan) using the flow system.

#### *Transmittance of the Polymer Mixture in Water at 600 nm*

A 0.02% (w/v) solution of MC100 and a 0.02% (w/v) dispersion of CP were prepared in distilled water, mixed together at various ratios, and degassed by sonication. MC-CP interpolymer complexation was studied by measuring the transmittance of the MC-CP aqueous mixture at 600 nm with a UV spectrophotometer (U-best 30, JASCO, Tokyo, Japan). A lower transmittance represents a larger amount of water-insoluble interpolymer complex.[18,19]

## RESULTS AND DISCUSSION

### *Physicochemical Properties of Solid Dispersions and Release Profiles of PHE From MC-CP Solid Dispersion Granules at Various MC/CP Ratios*

Figures 1 and 2 show the powder radiograph patterns and DSC curves of PHE, MC, and CP, with the physical mixture and solid dispersion of the MC/CP ratio at 50:50, respectively. MC100 (molecular weight, 180,000) was used. The PHE was 20% in the physical mixture and solid dispersion. MC and CP showed hollow radiograph diffraction patterns and no melting peak in the DSC curves, suggesting the amorphous polymers. In the physical mixture, the radiograph diffraction peak and the melting endothermic peak in the DSC curves based on PHE crystal were observed. These peaks almost disappeared in the solid dispersion. The same results were observed in other solid dispersions. Based on these results, it appears that, like MC and CP, PHE exists in an amorphous state in the solid dispersions.

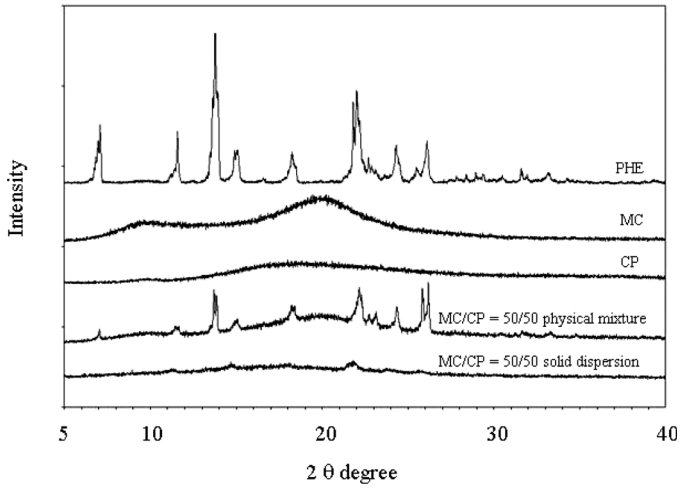


**Figure 1.** Powder radiograph patterns of PHE, MC, and CP and physical mixture and solid dispersion of the MC/CP ratio at 50:50. MC100 (molecular weight = 180,000) was used. The PHE was 20% in the physical mixture and solid dispersion.

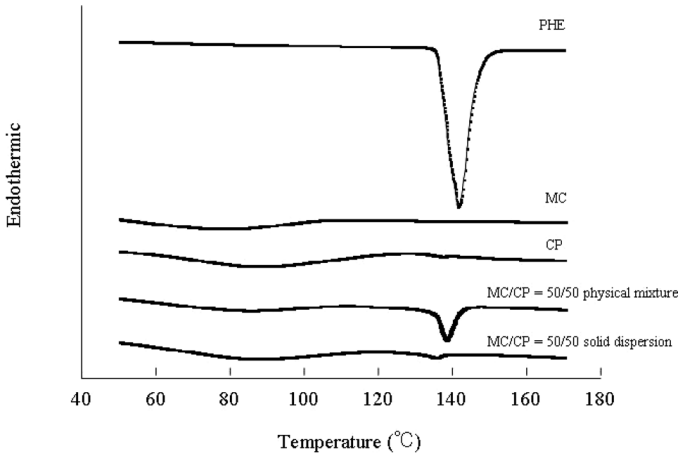


**Figure 2.** DSC curves of PHE, MC, and CP and physical mixture and solid dispersion of the MC/CP ratio at 50:50. MC100 (molecular weight = 180,000) was used. The PHE was 20% in the physical mixture and solid dispersion.

Figure 3 shows the release profiles of PHE from the PHE powder and the solid dispersion granules at the various MC/CP ratios. The rate of PHE release from the solid dispersion granules was lower than from the PHE powder. The PHE release profiles from the solid dispersion granules varied depending on the MC/CP ratio, and the rate of release was the lowest at a MC/CP ratio of 50:50.

Figure 4 shows the transmittance of the MC-CP aqueous mixture at various MC/CP ratios. MC100 (molecular weight, 180,000) was used. MC is a water-soluble polymer, whereas CP is a cross-linked and poorly soluble polymer. As a result, CP is not completely dissolved but, rather, is dispersed in water. The transmittance of the pure MC solution was 100%, indicating that it was transparent, and the transmittance of the pure CP aqueous dispersion was approximately 93%. In the case of the MC-CP mixtures, the transmittance was lower than for either MC or CP alone. The minimum transmittance was found at a MC/CP ratio of 50:50, indicating that this ratio results in the maximum amount of MC-CP complex formation. Although the reason for this is not clear, this ratio may result in the most efficient MC-CP complex formation in aqueous solution, as has been previously reported for complex formation between PEO and CP.[18,19] This MC/CP ratio may also result in the most efficient complex formation during the preparation of the solid dispersion, causing the lowest rate of PHE release.

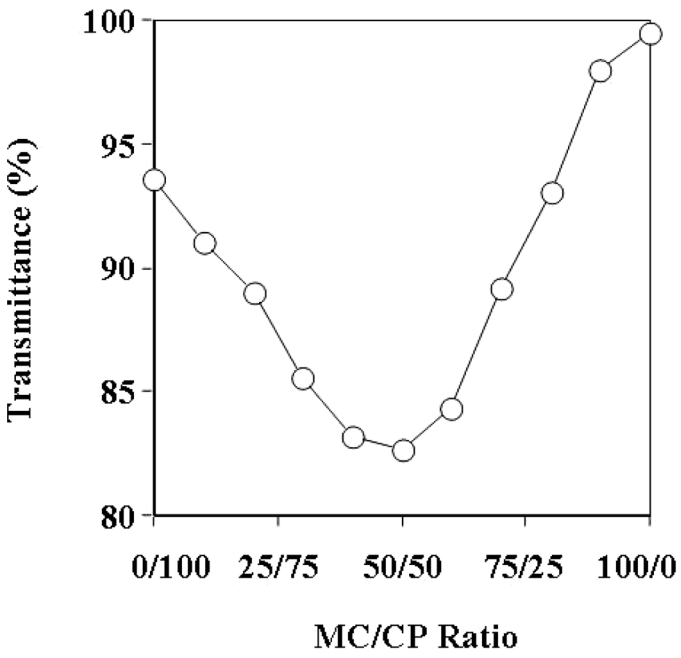


**Figure 4.** Transmittance of the MC-CP aqueous mixture at various MC/CP ratios. MC100 (molecular weight = 180,000) was used. Each point represents the mean ± SD (n = 3).

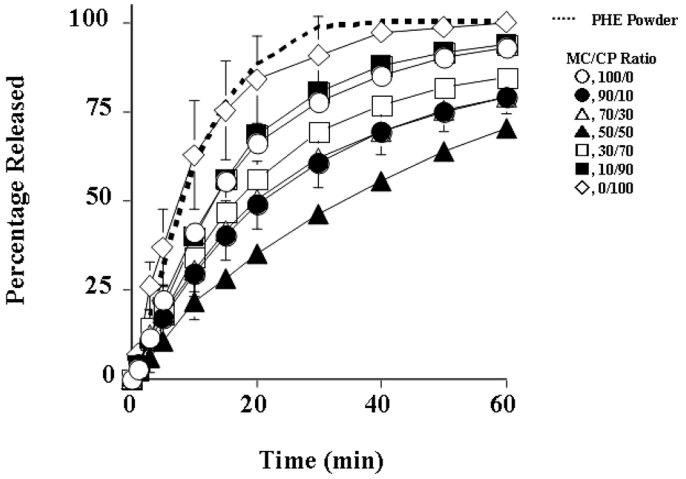


**Figure 3.** Release profiles of PHE from MC-CP solid dispersions with various MC/CP ratios. MC100 (molecular weight = 180,000) was used. Each point represents the mean ± SD (n = 3).

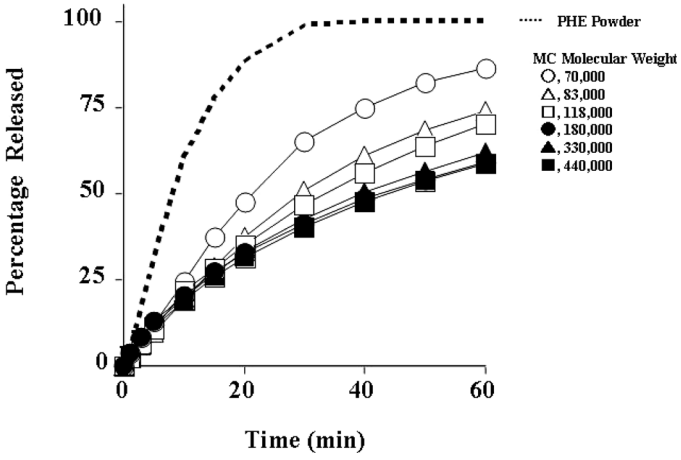


**Figure 5.** Release profiles of PHE from MC-CP solid dispersions using MC with various molecular weights. The MC/CP ratio was 50:50. Each point represents the mean ± SD (n = 3).

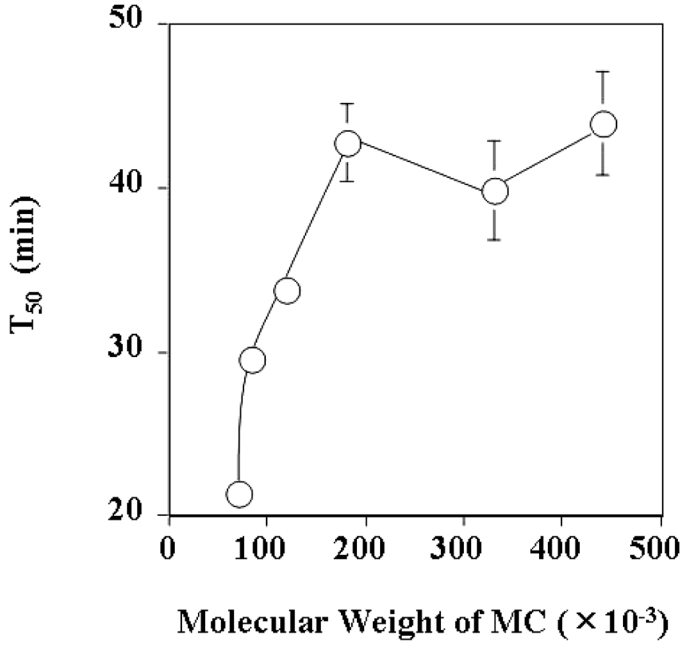


**Figure 6.** $T_{50}$ for PHE release from MC-CP solid dispersions using various molecular weights of MC. Each point represents the mean ± SD (n = 3).

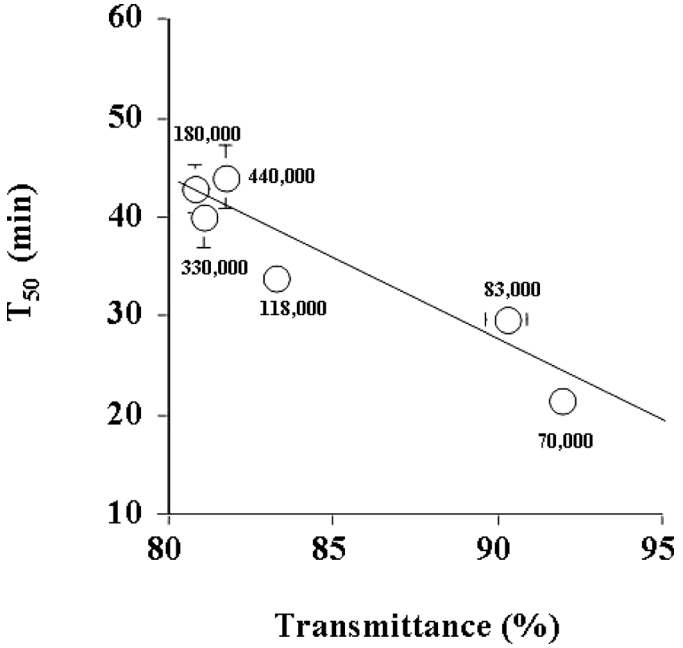


**Figure 8.** Relationship between the transmittance of the MC-CP aqueous mixture and $T_{50}$. The MC/CP ratio was 50:50. Each point represents the mean ± SD (n = 3).

### *Effect of Molecular Weight of MC on PHE Release From MC-CP Solid Dispersion Granules*

Figure 5 shows the profiles for PHE release from PHE powder as well as from solid dispersion granules with a MC/CP ratio of 50:50 and various molecular weights of MC. The rate of PHE release decreased as the molecular weight of MC increased. Figure 6 shows the effect of the molecular weight of MC on the time required to release half of PHE ($T_{50}$). The $T_{50}$ of the MC-CP solid dispersion increased as the molecular weight of the MC increased, and it essentially leveled off when the molecular weight of MC was ≥180,000. The transmittance of the MC-CP aqueous mixture (MC/CP = 50:50) at various molecular weights of MC is shown in Figure 7. The transmittance decreased as the molecular weight of MC increased, and, like the $T_{50}$, essentially leveled off when the molecular weight of MC was ≥180,000. These results indicate that

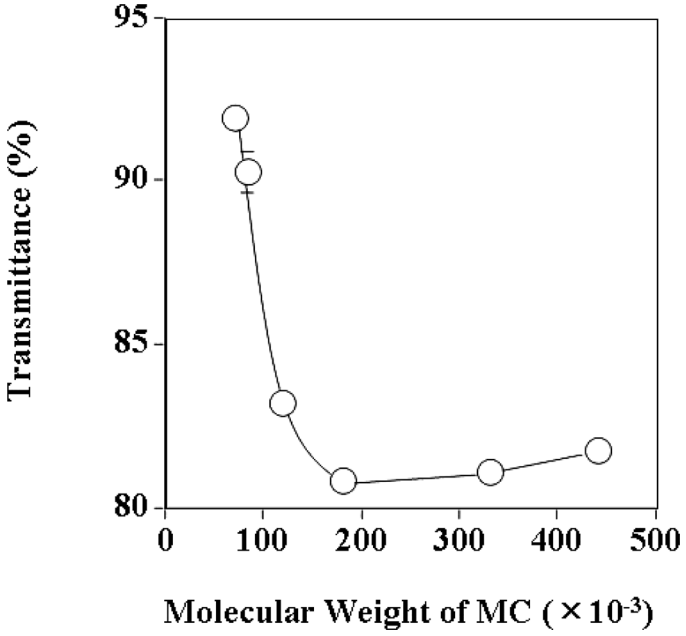


**Figure 7.** Transmittance of the MC-CP aqueous mixture at various molecular weights of MC. The MC/CP ratio was 50:50. Each point represents the mean ± SD (n = 3).

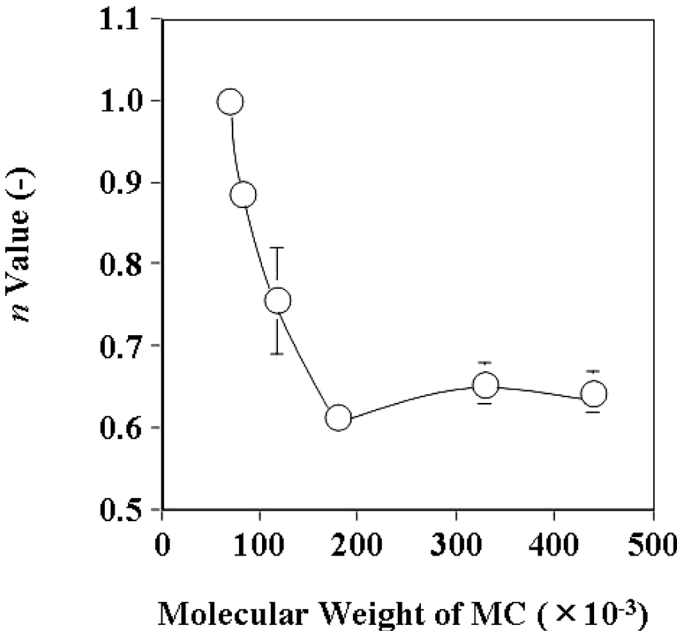


**Figure 9.** Plots of *n* versus the molecular weight of MC. Each point represents the mean ± SD (n = 3).

the efficiency of complex formation between MC and CP in water may increase as the molecular weight of MC rises, but that it does not change significantly when the molecular weight of MC is ≥180,000.

The interpolymer complex formation is reported to be attributable to cooperative effects that depend on the molecular weight of the polymer.[21,22] The initial reaction among the active sites on the polymer chains of different kinds occurs mostly by chance. Once a reaction among the active sites on the polymer chains is made, the adjoining active sites are brought closer, and the reaction rate of the following steps is accelerated. This process occurs successively, causing the complex formation to progress.[23-25] When the molecular weight is low, even if there is a local interaction between the polymer chains, it is difficult to cause conformational changes in the polymers, because the cooperative effect is small, resulting in little complex formation. The effect of cooperation increases with increasing polymer chain length, and the efficiency of complex formation increases. Therefore, more-efficient interpolymer complex formation may explain why the transmittance decreased as the molecular weight of MC increased. The effect of cooperative interaction is reported to reach a maximum when the polymer chain length becomes sufficiently long,[24] which can explain why the transmittance did not significantly change when the molecular weight of MC was increased to >180,000.

Figure 8 shows the relationship between the transmittance of the MC-CP aqueous mixture (MC/CP = 50:50) at various molecular weights of MC and the $T_{50}$ of PHE release. There was a good correlation between these 2 measurements ($r = 0.933$), and the $T_{50}$ increased as the transmittance decreased. The transmittance shows the complex formation of MC-CP in water but does not show the complex formation directly in the MC-CP solid dispersion. However, Figure 8 indicates that when MC had undergone efficient complex formation with CP in water, the rate of PHE release was lower than in the MC-CP solid dispersions. These results suggest that the MC-CP complex formation also occurred efficiently in the solid dispersion when we used forms of MC that efficiently complexed with CP in water. Thus, up to a molecular weight of 180,000, the rate of PHE release decreased as the molecular weight increased. Although it is unclear why the rate of release leveled off when the molecular weight of MC was ≥180,000, we suspect it is because this molecular weight gives the maximal cooperative effect between the MC and CP used in this study.

### *Mechanism of PHE Release Through MC-CP Solid Dispersions at Various Molecular Weights of MC*

To investigate the mechanism by which the molecular weight of MC controls the rate of release, we analyzed the data using the following semiempirical equation for drug release from polymer devices[26]:

$$F = Kt^n \quad (1)$$

where $F$ is the fractional release ($<0.6$) up to time $t$; $K$ is a kinetic constant; and $n$ is the diffusional exponent, which is indicative of the release mechanism. When $n$ is 0.5, drug release occurs by a diffusion-controlled process obeying the Fickian diffusion model. When $n$ is 1.0, the swelling or relaxation rate of the matrix polymer is the rate-determining step, and zero-order release is observed. When $0.5 < n < 1.0$, both Fickian diffusion and relaxation of the polymer contribute to the drug release.

The release data were fitted to the logarithm of equation 1, and the $n$ value was obtained from the slope of log $F$ versus log $t$ plots. As shown in Figure 9, the $n$ value was approximately 1.0 at the lowest molecular weight of MC, where the cooperative effects for complex formation are smallest. Because the portion of MC or CP that did not form a complex in the solid dispersion was hydrophilic, the swelling and relaxation of the polymers was the rate-determining step for the low-molecular weight forms of MC. As the molecular weight of MC increased up to 180,000, the $n$ value decreased so that $0.5 < n < 1.0$. At or above this molecular weight, the $n$ values leveled off. This result indicates that the contributions of diffusion and polymer relaxation to drug release increased as the molecular weight of MC increased. When the molecular weight of MC was ≥180,000, it appeared that the release mechanism did not change. This is likely because of saturation of the cooperative effect and, thus, the extent of complex formation.

## CONCLUSION

The release of PHE from the solid dispersion granules depended on the MC/CP ratio, with a ratio of 50:50 giving the lowest rate of release. At a MC/CP ratio of 50:50, the release of PHE from the solid dispersion granules decreased as the molecular weight of the MC increased, reaching a plateau at molecular weights ≥180,000. The contributions of diffusion and polymer relaxation to PHE release increased as the molecular weight of the MC increased. This study shows that it is feasible to control PHE release from MC-CP solid dispersions by controlling the complex formation between MC and CP. This can be accomplished by varying the MC/CP ratio and the molecular weight of the MC.

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