Preparation of a Directly Tabletable Controlled-Release Matrix Filler with Microcrystalline Cellulose Modified with Hydroxypropylmethylcellulose

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A controlled-release matrix filler was prepared by spray-drying a heated aqueous hydroxypropylmethylcellulose (HPMC) solution suspending microcrystalline cellulose (MCC, PH101). Acetaminophen tablets (used as model drug, content = 50%) were prepared by directly compressing the mixture of drug and spray-dried matrix filler. When HPMC was formulated with more than 10% of the matrix filler, drug release from the tablets was satisfactorily sustained. To obtain a similar sustained-release pattern with unmodified original HPMC, more than 50% of the matrix filler was required in the formulation. Whereas, when the tablet formulation was less that 5% modified HPMC, the drug was rapidly released from the tablets. Uniformly distributed HPMC in the spray-dried filler should lead to such drug-releasing behaviors. The micromeritic properties of HPMC in the matrix filler, *viz.* particle size, size distribution and the loading amount of HPMC, were main factors in determining the drug-release properties of the tablets. The drug-release rate of the tablets was determined by the erosion rate of the gelled HPMC formed on the surface of the tablets. The drug-release kinetics were described as a function of the cube root of the tablet weight. The drug was tabletted directly with the modified matrix filler by a rotary tabletting machine.

Keywords hydroxypropylmethylcellulose; controlled-release; matrix filler; direct tabletting; gelatinous layer; erosion behavior

Many controlled-release systems have been developed for maintaining a therapeutically effective concentration of drug in systemic circulation for a long period of time, as well as to reduce side effects. Oral controlled-release systems are mainly grouped into three types, *viz.* reservoir, monolythic and matrix types. The matrix device is preferable for computerizing the process for factory automation, since this device can be prepared simply by mixing the drug with a matrix base, followed by compression. Cellulose derivatives are the most commonly used hydrophilic polymers for oral controlled-release tablet formulations. There are several articles discussing the use of water-soluble polymers as hydrophilic gel-forming materials to control drug-release rate, which depends on the viscosity of the gel,[1-3] particle size[1,4] of the polymer, solubility of the drug,[5] and the mixing ratio of polymer to drug.[1-3,6] Hydroxypropylmethylcellulose (HPMC) and hydroxypropylcellulose (HPC) are recommended matrix filler for obtaining a reliable drug-releasing tablet, because the drug-release rate from the matrix tablet is independent of the compression pressure used to prepare the matrix,[2,7] the hardness of the tablet,[7,8] and the pH of the medium.[8]

Low-substituted HPC (L-HPC) is widely used as a binder and a disintegrant, due to its excellent binding and swellable properties. Recently it was found, surprisingly, that L-HPC acted as a sustained-release matrix base when it was pulverized (average particle size $\leqq 4.4\,\mu m$) and loaded in the formulation at a content higher than 20%.[9,10] In a previous report,[10] the mechanism of prolonged drug release behavior was explained in terms of a gel-like layer formed on the surface of matrix tablets with a water soluble compound of the pulverized L-HPC, *e.g.* HPC, which dramatically reduced the penetration rate of water into the matrix tablets. However, it was difficult to directly employ pulverized L-HPC for practical tabletting, due to its poor flowability and packability.[11] Granulations were required to improve the micromeritic properties of the pulverized L-HPC.[11]

The purpose of the present study was to prepare a directly compressible controlled-release matrix filler, for tabletting with a drug, by physically modifying microcrystalline cellulose (MCC) with HPMC using a spray-drying technique. MCC was formulated because it has been accepted as an excellent powdered binder for the direct tabletting process.[12] The drug-release behavior of the tablets, combining a various spray-dried matrix fillers and the drug, were investigated to find an optimum spray-drying formulation. Finally, a practical formulation with the most suitable matrix filler was tabletted by a rotary tabletting machine to prepare the controlled-release matrix tablet.

Materials and Methods

Materials HPMC (60SH-4000, average particle size = 45.6 μm) and MCC (PH101, average particle size = 45.7 μm), as original matrix fillers, were obtained from Shin-Etsu Chemical, Japan and Asahikasei Industry, Japan, respectively. Acetaminophen (average particle size = 185.0 μm) as a model drug was supplied by Yamamoto Chemical, Japan. Those average particle sizes were determined by a sieving method using the standard sieves specified in JP XII. Light anhydrous silicic acid (Aerosil 200, Nippon Aerosil, Japan) and magnesium sterate (Kishida Chemical, Japan) as a glidant and a lubricant, were used, respectively.

Preparation of Controlled-Release Matrix Fillers The controlled-release matrix fillers were prepared by spray-drying the following three feeding solutions.

(I) Low viscous HPMC aqueous solution (0.5%, w/v) suspending PH101 was prepared for direct spray-drying, termed the solution method.

(II) High viscous HPMC aqueous solution (1—2%, w/v) suspending PH101 was warmed up to 80 °C to reduce the viscosity, and then the warmed solution was spray-dried, termed the warmed-solution method.

(III) HPMC and PH101 were suspended in distilled water warmed up to 80 °C, and then the prepared suspension was spray-dried, termed the warmed-suspension method. HPMC was not soluble in water warmed more than about 70 °C.

The operating conditions of the spray dryer (model L-12, Ohkawara Kakoki, Japan) were: the inlet and outlet air temperatures, 210 °C and 110 °C, respectively, the feeding speed of liquid of 50 ml/min, and the atomizing wheel rotated at 15000 rpm. Spray-dried fillers sieved through 42 mesh (355 μm) were used as controlled-release matrix fillers. The

TABLE I. Composition of Feeding Liquid for Spray-Drying and Micromeritic Properties of Modified Matrix Fillers

	Solution method							Warmed-solution method			Warmed-suspension method
	A	B	C	D	E	F	G	H	I	J	K
Composition											
HPMC (g)	0	2.5	5	10	15	20	100	10	15	20	20
PH101 (g)	100	97.5	95	90	85	80	0	90	85	80	80
Distilled water (L)	0.5	0.5	1	2	3	4	20	1	0.75	1	1
Micromeritics[a] ($n=3$)											
Angle of repose (°)				43	47	48		39	39	41	
Bulk density (g/cm^3)				0.193	0.118	0.102		0.315	0.294	0.204	
Average particle size (μm)				80.0	84.5	83.6		71.7	69.6	66.3	

a) All of the modified matrix fillers were sieved through 42 mesh (355 μm).

composition of these modified matrix fillers and their micromeritic properties are tabulated in Table I. It was found that there were no differences in the X-ray diffraction patterns of any of the modified or unmodified matrix fillers.

Preparation of Tablets and Measurement of Their Crushing Strengths The tablets were prepared by the following two methods.

(I) The physical mixtures (about 200 mg) of acetaminophen and either the modified matrix filler or the unmodified matrix filler (original mixture of PH101 and HPMC), with various weight ratios (usually 1 : 1 unless otherwise mentioned), were directly compacted using an Instron-type hydraulic press (Autograph AG-5000D, Shimadzu Corporation, Japan) under a compression pressure of 200 MPa, using flat-faced punches and a die with a diameter of 8.0 mm.

(II) The physical mixture of acetaminophen (50%) and modified matrix filler (49.6%), produced by the warmed-solution method, was mixed with Aerosil 200 (0.1%) and magnesium stearate (0.3%) and compacted continuously using a rotary tabletting machine (type: RT-F-9-2, Kikusui Seisakusho, Japan) equipped with nine paired flat-faced punches in a die, with diameters of 8.0 mm, operated at a rate of 10 rpm. The compression pressure was set at about 200 MPa. The true applied compression pressure was measured with a strain gauge (load cell) attached to the lower roller. The mean weight, weight deviation and coefficient of variation of the tablets (designed weight, 200 mg), sampled randomly, were calculated.

Tablet crushing strength was represented by the force required to fracture the tablet under diametrical compression (Autograph AG-5000D, Shimadzu Corporation, Japan). The value of crushing strength used was the mean of ten runs.

Dissolution Test of Tablets A JP XII dissolution paddle assembly (type: NTR-VS6P, Toyama Sangyo, Japan) with 900 ml of distilled water was used. The dissolution medium was temperature-controlled at 37±0.5 °C and stirred constantly at 100 rpm. The concentration of acetaminophen dissolved in the medium was measured by a spectrophotometer (model 100-60, Hitachi Manufacturing, Japan) set at 244 nm (λ_{max}). T_{50}, the time required for 50% of the drug to be released, was obtained from a dissolution profile of the drug released against time. Dissolution tests were performed in triplicate for each tablet. The standard deviations were exhibited at each datum in Figs. 3, 4 and 5.

Micromeritic Properties of Modified Matrix Fillers The average particle size of the modified fillers was determined by a laser scattering light analysis system (LDSA-2400A, Tohnichi Computer, Japan) using a dispersing-in-air method on a volume basis. The angle of repose of the modified matrix fillers was measured by a repose angle tester (type: Konishi-FK, Konishi Seisakusho, Japan). The samples were passed carefully through a funnel to form a stable cone. The lower tip of funnel was maintained at a height of 10 cm from the surface of the plate throughout the test. The angle of repose was directly measured by a graduator. The bulk density of the samples was determined by a tap density tester (type: RHK, Konishi Seisakusho, Japan). A sample of about 12 g of granules was carefully introduced into a 50 ml graduated cylinder. The cylinder was dropped 3 times from a height of 2.5 cm in 2-second intervals. The bulk density was then obtained by dividing the weight of the sample by the volume of the sample contained in the cylinder. All of the above data, listed in Table I, are the mean values of three runs.

Results and Discussion

Comparison of the Controlled-Release Functions of Modified Matrix Fillers Produced by Spray-Drying Methods

The drug-release profiles of tablets prepared with a physical mixture of acetaminophen and each modified matrix filler, produced by the solution method as listed in Table I, is shown in Fig. 1. The unmodified original matrix filler of PH101 and HPMC mixture, with a weight ratio of drug and filler = 1 : 1, is also shown in Fig. 1. The tablets exhibited a sustained-release behavior when the amount of HPMC was more than 10% in the modified matrix fillers. On the other hand, more than 50% of HPMC in the unmodified matrix fillers was required for sustaining the drug release of the tablets. The sustained-release function of the modified filler was created even with a low-loading of HPMC (10—20%), compared to that of the unmodified matrix filler. It was assumed that HPMC particles in the modified matrix filler were more uniformly distributed than in the unmodified filler. The more dispersed HPMC particles had a larger specific surface area than the aggregated HPMC particles in the unmodified matrix fillers, and easily formed a continuous layer in the tablets. Therefore, in the tablets of the modified matrix fillers, a more uniform gelatinous layer in the tablet was formed, which helped to sustain the drug release. However, the tablets of the modified matrix filler or its unmodified matrix filler containing HPMC of $\leqq$5% or $\leqq$30%, respectively, showed a rapid-release of the drug due to the swelling of HPMC and subsequent formation of water channels, resulting in the disintegration

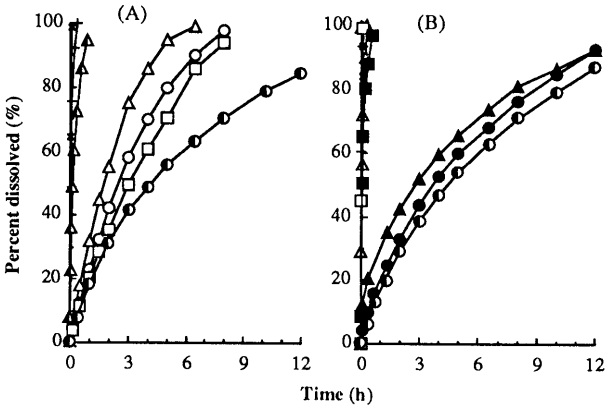

Fig. 1. Drug-Release Profiles of Tablets prepared with Acetaminophen (50%) and Matrix Fillers (50%) Using the Autograph

The matrix fillers used are (A) modified matrix fillers, produced by the solution method, as listed in Table I, and (B) unmodified matrix fillers, in various composition ratios of PH101 to HPMC, (▲) 100:0, (×) 97.5:2.5, (+) 95:5, (△) 90:10, (○) 85:15, (□) 80:20, (■) 70:30, (▲) 50:50, (●) 30:70 and (◐) 0:100.

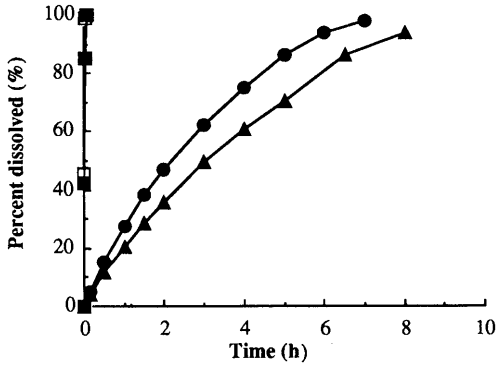

Fig. 2. Drug-Release Profiles of Tablets Prepared with Acetaminophen (50%) and Modified Matrix Filler (50%) ((▲) F, (●) J or (■) K Listed in Table I), or (□) Its Unmodified Matrix Filler Using the Autograph

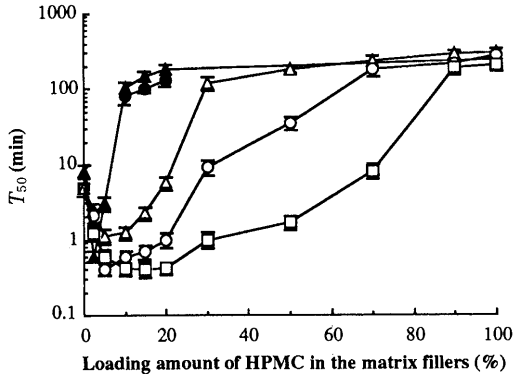

Fig. 3. Effect of Particle Size of HPMC and Its Loading Amount on the Drug-Release Rate (T_{50}) of Tablets Prepared with Acetaminophen (50%) and Matrix Fillers (50%) Using the Autograph

The matrix fillers used are modified matrix fillers, produced by the (▲) solution method and (●) warmed-solution method, as listed in Table I, and unmodified matrix fillers containing HPMC with a particle size (□) over 200 mesh, (○) 300 to 400 mesh and (△) below 400 mesh.

of the tablets.

Figure 2 shows the drug-release profiles of the tablets prepared with modified matrix fillers produced by both the warmed-solution method and the warmed-suspension method for reducing the viscosity of the HPMC solution for spray-drying. The modified matrix fillers produced by the warmed-solution method possessed a similar sustained-release function to that produced by the solution method, although the drug-release rate of the former tablets was slightly faster than that of the latter. On the other hand, the modified matrix filler produced by the warmed-suspension method yielded rapid-releasing tablets, as was found with the unmodified matrix filler. It was due to the fact that HPMC was not soluble, but suspended in the warmed-water. HPMC and PH101 were mixed simply in the spray-drying process, resulting in a physical mixture similar to the unmodified matrix filler. The findings in Figs. 1 and 2 indicate that the distribution of HPMC in the matrix filler, depending on the particle size and the loading amount of HPMC, was an important factor in determining the drug-release properties of tablets.

To elucidate the physicochemical characteristics of HPMC in the modified matrix fillers, the effects of particle size and loading amount of HPMC in the modified matrix fillers on the drug-release properties of the tablets were investigated in the following paragraph.

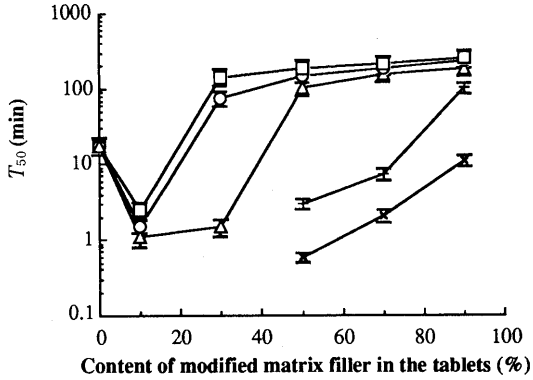

Fig. 4. Effect of the Content of Modified Matrix Filler on the T_{50} of Tablets Prepared with Various Ratios of Acetaminophen and Modified Matrix Filler Using the Autograph

Symbols of the ratios of PH101 to HPMC in the modified matrix fillers, produced by the solution method, are the same as shown in Fig. 1.

Effects of Particle Size and Loading Amount of HPMC on the Drug-Release Properties of Tablets The effects of particle size and loading amount of HPMC in the matrix filler on the drug-release rate (T_{50}) of tablets, prepared with acetaminophen and either modified matrix filler or original unmodified matrix filler, are shown in Fig. 3. The T_{50} of the tablets increased with increasing the loading amount of HPMC in the unmodified matrix fillers, when the loading amount of HPMC $\geqq$ 10 to 20%. The degree of increase with the loading amount depended on the particle size of HPMC, *viz.* the degree increased as size decreased. The T_{50} of tablets with same loading amount of HPMC increased with a decrease in the particle size of HPMC, as discussed in Figs. 1 and 2 in the previous paragraph. To sustain the drug-release rate with the unmodified matrix fillers, more than 30%, 70% or 90% of HPMC, should be loaded into the matrix filler depending on the particle size, *i.e.* 400 mesh pass, 300 to 400 mesh or 200+ mesh, respectively. It was assumed that when the aqueous solution of HPMC was spray-dried, fine HPMC particles were deposited uniformly on the surface of MCC during drying. Because of this characteristic structure of modified matrix filler, the sustained-releasing property of the tablet with modified matrix filler was obtained with a lower loading amount of HPMC required.

The effects of the content of modified matrix filler formulated in the tablet on the drug-release rate (T_{50}) are shown in Fig. 4. The T_{50} increased as the content of modified matrix filler ($\geqq$10 to 50%) increased, depending on the amount of HPMC in the matrix filler. At a lower content ($\leqq$10%) of the modified matrix filler containing HPMC (10 to 20%), the tablet rapidly released the drug through a water channel formed by a swelling of HPMC, as discussed in Fig. 1. With the same content of modified matrix filler in the tablet, T_{50} increased as the loading amount of HPMC in the modified matrix filler increased. To clarify the effect of the loading amount of HPMC in the tablet on the drug-release rate, the correlation between T_{50} and the loading amount of HPMC in the tablets was plotted in Fig. 5. As can be seen, the tablets containing modified more than 5% HPMC in weight showed a sustained-release behavior, whereas more than 25% of unmodified HPMC was required to be compounded in the tablet in order to

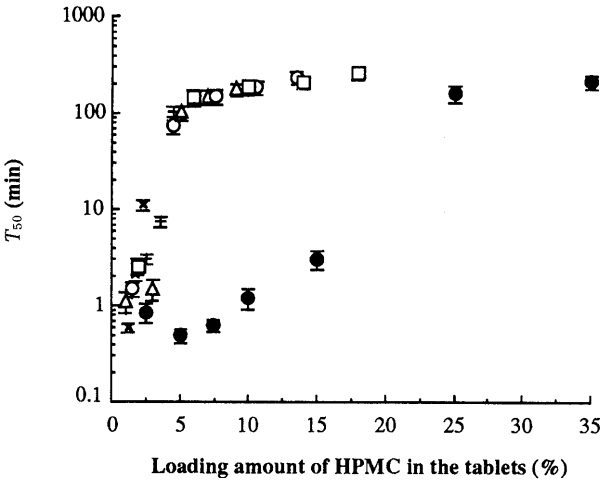

Fig. 5. Correlation between the T_{50} and the Loading Amount of HPMC of the Resultant Tablets, Obtained the Same Result Shown in Fig. 4

The plots (closed symbols) are from the data shown in Fig. 1B.

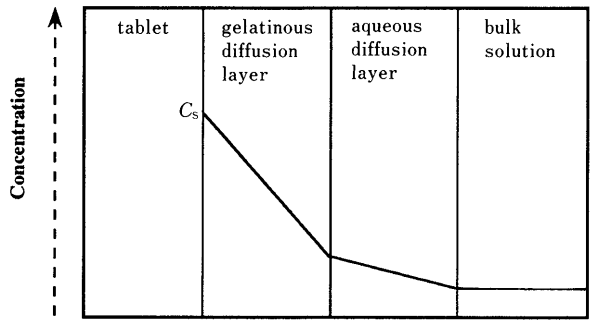

Fig. 6. Dissolution Model from the Tablet

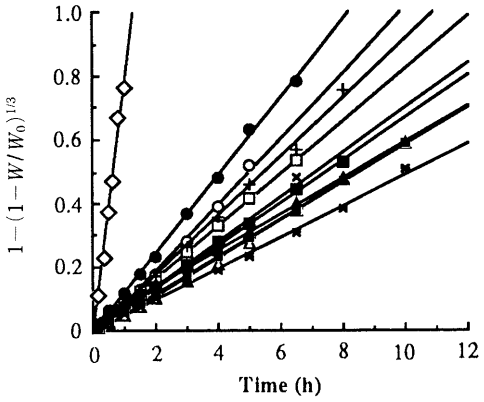

Fig. 7. Drug-Release Kinetics of the Resultant Sustained-Release Tablets as a Function of the Dissolution Rate Eq. 1

$r^2=0.994$. HPMC/PH101/drug: ◇ 0/0/100; ● 5/45/50; ○ 7/63/30; ■, 9/81/10; □ 7.5/42.5/50; ▲ 10.5/59.5/30; △, 13.5/76.5/10; +, 6/24/70; × 10/40/50; ■ 14/56/30; ⋈, 18/72/10.

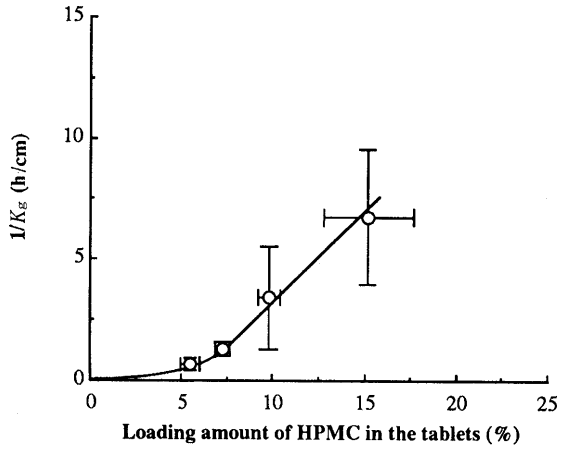

Fig. 8. Correlation between the $1/K_g$ and the Loading Amount of HPMC in the Tablets ($n=2$—3)

sustain the drug-release rate. The results indicate that the loading amount of HPMC in the tablets is a main factor in controlling the drug-release rate of the tablets, *i.e.* from rapid- to sustained-release at lower and higher loading rates, respectively. Further uniform distribution of HPMC in the tablet must be required to impart a satisfactory sustained-releasing property to the tablet. This was accomplished by depositing HPMC uniformly on the surface of a MCC particle by a spray-drying process.

Drug-Release Kinetics of Sustained-Release Tablets with Modified Matrix Filler It is well known that hydrated hydrogel matrices can form a gelatinous layer which can control the diffusion of a drug. The drug-release kinetics of such hydrogel matrix tablets were described in terms of zero-order, first-order, Fickian and non-Fickian release mechanisms,[3,5,13] depending on the properties of the erosion (or dissolution) of gel layers in the system. In the present study, it was found that the tablets decreased in size isotropically without disintegration, when more than 5% modified HPMC was loaded in the tablet. It was assumed that the drug was released through a diffusion layer consisting of aqueous and gelatinous layers on the surface of the tablet, which remained intact until the complete dissolution of the tablet, as described in Fig. 6. Kawashima *et al.*[14] introduced the following equation (Eq. 1), describing the amount of drug released through a diffusion layer of the erosible tablet, assuming the diffusion layer remained constant on the surface of the tablet.

$$1-(1-W/W_0)^{1/3}=k_a t \quad (1)$$

$$k_a=K\cdot\pi C_s/6W_0\cdot(1+2l_0/d_0)\cdot d_0^2$$

where W_0 is the original drug content in the tablet, W is the drug amount dissolved at the release time (t), k_a is the apparent dissolution rate constat, C_s is the drug solubility, and l_0 and d_0 are the original tablet thickness and diameter, respectively. Equation 1 was applied to explain the dissolution data (5% ≦ percent dissolved ≦ 95%) of the tablets, as shown in Fig. 7. Linear relationships for all data were found ($r^2 \geqq 0.994$). It was proved that the drug-release kinetics of tablets was described by the erosion of the tablet. The apparent dissolution rate constant (k_a) decreased as the amount of HPMC loaded in the tablet increased. It was assumed that the mass transfer coefficient in the aqueous diffusion layer ($K_d=D/X$) was constant, even if the loading amount of HPMC in the tablets was changed, as long as the dissolution test conditions were the same, *e.g.* agitation speed of the paddle, volume of the dissolution medium, and temperature of the dissolution medium; because, the diffusion coefficient of drug through the aqueous diffusion layer (D) and the thickness of aqueous diffusion layer (X) were constant under such conditions.[15] K_d can be estimated from the dissolution test of the tablet prepared with the drug only. The diffusional resistance ($1/K_g$) of the gelatinous layer

TABLE II. Properties of Tablets Prepared Continuously by a Rotary Tabletting Machine

	Tablet[a]		
	I	II	III
Tablet weight[b] (mg)	204.1±3.3	206.5±4.0	203.0±5.2
Coefficient of variation (%)	1.7	1.9	2.7
Deviation range (%)	−2.1—3.6	−2.7—3.6	−3.1—5.0
Crushing strength (N)	36.3±2.3	38.2±3.1	38.5±3.6

a) Tablets (I, II and III) prepared with modified matrix filler (H, I and J listed in Table I, respectively). *b*) Mean±S.D. ($n=20$).

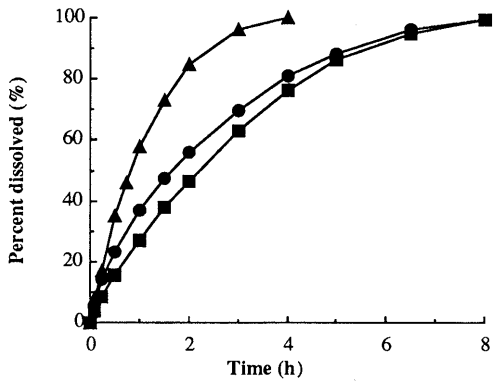

Fig. 9. Drug-Release Profiles of Tablets Composed of Acetaminophen (50%), Modified Matrix Filler (49.6%) ((▲) H, (●) I or (■) J Listed in Table I), Aerosil 200 (0.1%) and Magnesium Stearate (0.3%) Prepared Using a Rotary Tabletting Machine

can be calculated by the relationship, *viz.* $1/K=1/K_d+1/K_g$, where K_d was found to be 0.37 (cm/h) and K is the overall mass transfer coefficient. $1/K_g$ is plotted against the loading amount of HPMC in the tablet, as shown in Fig. 8. The diffusional resistance of the gelatinous layer increased with increasing the loading amount of HPMC in the tablet. By increasing the amount of HPMC in the tablet, a mechanically stronger gel might be produced, resulting in a thicker layer. Further, the diffusion of the drug through the gelatinous layer decreased as a result of increasing the viscosity of the gelatinous layer.

Preparation of Controlled-Release Tablets Using a Continuous Rotary Tabletting Machine Modified matrix fillers produced by the warmed-solution method had better flowability and packability than those produced by the solution method, as listed in Table I. The warmed-solution method saved spray-drying time compared to the solution method, which required two to four times longer to evaporate the aqueous media than warmed method. Therefore, the modified matrix fillers produced by the warmed-solution method were employed to directly prepare the controlled-release tablet using a rotary tabletting machine. The properties of the resultant tablets are shown in Table II. The weight deviations and coefficients of three types of tablets met the requirements specified in the JP XII. The tablets satisfactorily sustained the drug release, as expected from the results in Fig. 1. The order of sustained-release followed the amount of HPMC loaded in the formulation, as expected.

In conclusion, novel controlled-release matrix fillers for direct tabletting were successfully developed by modifying MCC with soluble polymer, *e.g.* HPMC. They can be easily prepared on an industrial scale by using a spray dryer and employed practically with a rotary tabletting machine. It was possible to prepare matrix fillers which varied widely, from rapid- to sustained-release systems, by controlling the amount of HPMC in the formulation during spray-drying. Further, drug-release behaviors could be controlled by the content of modified matrix fillers in the tablet. In addition to using PH101 and HPMC, we are trying to find other matrix fillers by these applying present principles to prepare a controlled-release tablet by the direct tabletting process.

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