Sustained-Release Matrix Using Hydroxypropylcellulose–Ethylcellulose Complex as a Filler, and Controlling Factors of Drug Release

Shigeru AOKI,* Hidenobu ANDO, Ryoichi MACHIDA, Katsumi IDA, Sumio WATANABE, and Hiroshi OZAWA

Department of Pharmaceutical Research, Eisai Co., Ltd., Takehaya-machi 1, Kawashima-cho, Hashima-gun, Gifu 501-61, Japan. Received January 20, 1993

The effect of formulation variables on the release rate of phenylpropanolamine hydrochloride (PPA) from hydroxypropylcellulose (HPC)–ethylcellulose (EC) complex was investigated. With an increase in the weight fraction of HPC (WFH) in the filler, drug release from the solid made from a dissolved mixture of HPC and EC (SMH) tended to decrease. The major controlling factors appeared to be WFH in the filler, the HPC viscosity grade, and the PPA: filler ratio. When a low viscosity grade of HPC (HPC-L) was used, the release rates from the SMH matrix were greater than those from the physically mixed matrix at less than 50% WFH. EC particles obtained from SMH after a 6-hour dissolution test possessed a number of pores. It was assumed that after dissolving HPC-L from the SMH filler, the porous EC particles might promote drug release because the number of water channels increased. Variation in the compression pressure in the tablet manufacturing process was an insignificant factor in the drug release rate. A linear relationship was observed between the release rate and the reciprocal amount of filler. Furthermore the release rate as a function of surface area of the tablet was also in good relationship. With these relationships, the composition of the tablet can be predicted to obtain the demand release rate of the drug.

Keywords phenylpropanolamine HCl; hydroxypropylcellulose; ethylcellulose; release control factor; release rate

Controlled-release systems have been developed for the purposes of maintaining a therapeutically effective concentration of drug in the systemic circulation for a long period of time, and for reducing the side effects of a single dose. A number of methods and techniques have been used in the manufacture of oral controlled-release dosage forms. The direct compression technique is a simple and well-known technique for formulating controlled release dosage forms, incorporating the drug into a matrix tablet of hydrogels. Hydrogel hydrates on contact with water, and water-soluble drugs are released by diffusion out of the gelatinous layer or by erosion of the gel, whereas poorly soluble drugs are released solely by erosion.[1] Generally, their release rate modulation is achieved using different grades of polymers,[2] different types of polymers,[3] soluble fillers,[4] or insoluble fillers.[5]

In our previous paper,[6] a solid made from a dissolved mixture of the hydrogel (SMH), composed of hydroxypropylcellulose (HPC) and ethylcellulose (EC), showed better flowability and hygroscopicity than HPC alone. Therefore, the use of SMH is acceptable as a filler for the matrix formulation. When a drug is compressed into tablets with SMH having different weight fractions of HPC (WFH), the rate of drug release may vary.

In this study, SMH was used as a controlled-release filler, being compressed into tablets with phenylpropanolamine HCl (PPA) as a model drug. We investigated the influence on the drug release rate of several drug controlling factors; PPA: filler ratio, WFH in the filler, HPC viscosity grade and manufacturing process of the filler.

Experimental

Materials PPA was obtained from ALPS Pharmaceutical Ind. (Gifu, Japan). HPC (Nihon Soda, Tokyo, Japan) of three viscosity grades was used; HPC-H, HPC-M and HPC-L (2320, 280 and 8 cps viscosity grade, respectively; the viscosity of an aqueous solution containing 2% by weight of dry HPC at 20°C was measured). EC (10 cps viscosity grade, Dow Chemical, U.S.A.) used was sieved by passage through a 150-mesh screen (105 μm). HPLC-grade acetonitrile was used in the HPLC mobile phase preparation. All other chemicals used in the analyses were of a reagent grade.

Preparation of SMH Powders A 5% (w/w) ethanolic solution of HPC-H, and a 10% (w/w) ethanolic solution of EC were prepared. These solutions were mixed in the following HPC-H to EC weight ratios; 9:1, 4:1, 2:1, 1:1, 1:2 and 1:4, where WFH in the filler was 90, 80, 67, 50, 33.3 and 20%, respectively. The ethanol was then evaporated and SMH flakes were obtained. The SMH flakes were pulverized by a hammer mill to obtain SMH powder. The procedures are described in detail in our previous paper.[6] Three viscosity grades of HPC; HPC-H, HPC-M and HPC-L, were used to prepare SMH powders, and the three SMH powders thus made were named SMH-H, SMH-M and SMH-L, respectively.

Preparation of Physical Mixture of Hydrogel (PMH) Powder Commercial HPC and EC which had been passed through a 150-mesh (105 μm) sieve were blended in a mixer (Kyouritsurikou, Tokyo, Japan) to obtain

TABLE I. Composition of Tablet (I—XXI)

Material	I	II	III	IV	V	VI
PPA	40	40	40	40	40	40
SMH-H[a]	200	—	—	—	—	—
SMH-M[a]	—	200	—	—	—	—
SMH-L[a]	—	—	200	—	—	—
PMH-H[b]	—	—	—	200	—	—
PMH-M[b]	—	—	—	—	200	—
PMH-L[c]	—	—	—	—	—	200

Material	VII	VIII	IX	X	XI	XII	XIII	XIV
PPA	40	40	40	40	40	40	40	40
SMH-H[d]	150	100	300	400	500	600	700	800

Material	XV	XVI	XVII	XVIII	XIX	XX	XXI
PPA	21.1	42.1	63.2	84.2	105.3	147.4	189.5
SMH-H[d]	78.9	157.9	236.8	315.8	394.7	552.6	710.5

a) WFH of filler; 20, 33.3, 50, 66.7, 80, 90%. *b*) WFH of filler; 0, 10, 15, 20, 33.3, 50, 66.7, 75, 80, 85, 90, 100%. *c*) WFH of filler; 0, 10, 15, 20, 33.3, 50, 66.7, 80, 90, 100%. *d*) WFH of filler; 20, 50, 80%.

PMH. The three HPC viscosity grades mentioned above were used to prepare PMH powders, and the three PMH powders were named PMH-H, PMH-M and PMH-L, respectively.

Preparation of Tablets PPA was mixed with fillers in various ratios (Table I) and directly compressed into flat-faced tablets (7.98 mm diameter) using a compression instrument (Autograph IS-5000, Shimadzu, Kyoto, Japan) at 196 MPa, except in the studies on the effect of pressure on release rate.

Effect of Formulation Factors To examine the effect of formulation factors on drug release, variously formulated tablets were used in the following studies; a) the effects of the viscosity grade of HPC and the manufacturing method of the filler on drug release (formulation I—VI), b) the effect of the compression pressure on drug release (formulation VII), c) the effect of the amount of filler on drug release (formulation I and VII—XIV), and d) the effect of the amount of matrix on drug release (formulations XV—XXI).

Dissolution Studies Tablets of each formulation were subjected to dissolution using a JPXII dissolution apparatus 2 (DT-600 dissolution tester, Freund-Jusco, Tokyo, Japan) in 900 ml of distilled water (pH 5.5—6) maintained at 37 ± 0.5 °C and with the paddle rotating at 100 rpm. At each sampling interval, an aliquot of the dissolution medium was drawn off and assayed by HPLC (LC-6A series, Shimadzu, Kyoto, Japan) with UV detection at 220 nm. The mobile phase used was acetonitrile–0.05 N potassium-2-hydrophosphate aqueous solution (5:95) at a flow rate of 1.5 ml/min through a C_{18} column (YMC-Pack FL-ODS3 column, 5 cm × 4.6 mm, 3 μm, Yamamura Chemical Lab., Kyoto, Japan). The volume of the solution was kept constant by replacing the sample volume with an equal volume of the dissolution medium. After sampling was completed, the drug was completely released from the tablet by grinding it with a spatula, and the medium was then assayed by HPLC. This value was taken as 100% of the dissolved amount.

Analyses of PPA Release The release kinetics of the drug from matrix tablets was analyzed by application of the Higuchi equation, Eq. 1,[7]

$$f_t = k_1 t^{1/2} + C \quad (1)$$

where f_t represents the amount of dissolved drug (%) at time t, k_1 (%min$^{-1/2}$) is the Higuchian release rate constant, and C is the y intercept of linear regression for the equation. Regression analysis was performed for up to 80% of the dissolved amount.

In order to understand the mode of drug release from swellable matrices, the data ($f_t < 60\%$) were fitted to the following simple exponential equation proposed by Korsmeyer *et al.*,[8] Eq. 2,

$$M_t/M_\infty = f_t/100 = k_2 t^n \quad (2)$$

where M_t/M_∞ is the fraction of drug released up to time t, k_2 (min^{-n}) denotes a constant incorporating the structural and geometric characteristics of the release device, and n is the release exponent indicative of the release mechanism. Eq. 1 is useful to clarify the release rate of the drug from the matrix, whereas Eq. 2 is helpful to interpret the mode of drug release.

Photomicrographs In SMH-L matrix tablets, after 6-hour dissolution studies, EC particles were collected by centrifugation, dried at 80 °C and subjected to scanning electron microscopy (SEM, JEOL Ltd., Tokyo, Japan). The EC particles and commercial EC passed through a 150 mesh (105 μm) sieve were observed under SEM.

Results and Discussion

Release Profiles of the Matrices PPA was used as the model drug for a controlled-release dosage form. PPA is a chemically stable, freely soluble compound. Alderman reported that a water-soluble drug is released by diffusion out of the gelatinous layer and by erosion of the gel.[1] Therefore, both diffusion and erosion should contribute to the PPA release rate from the tablet. In a previous study, these tablets demonstrated the advantages of pH- and agitation-independent release performance using the paddle method.[9] In the present study the dissolution test was performed with distilled water at 100 rpm. Figure 1 shows an example of the PPA release curves from matrices containing 90, 50 or 20% of the weight fraction of HPC-H (WFHH) in SMH-H filler. The curvilinear arrangement of the plots in the figure suggests that the release process obeys the Higuchian equation. This indicates that the dissolution rate of the drug is dependent on diffusion through the matrix. The plots also demonstrate that the drug release rate decreased as WFHH increased.

Effect of WFH on Drug Release The release kinetics from matrices composed of various WFHH of SMH-H was analyzed using Eqs. 1 and 2 as shown in Table II. Lapidus and Lordi stated that when release from a whole tablet, rather than from a plane surface, was analyzed using Eq. 1,[10] linearity was not maintained, since attrition or erosion of the hydrated layer influenced the drug release rate, k_1. Therefore, for Eq. 1, regression analysis was performed for up to 80% of the dissolved amount. Good linearity was obtained for Eq. 1. From Table II, k_1 decreased with an increase in WFHH of SMH-H. To investigate the mechanism of drug release, Eq. 2 was applied. Peppas stated that for the determination of the release exponent, n, only the initial portion of the

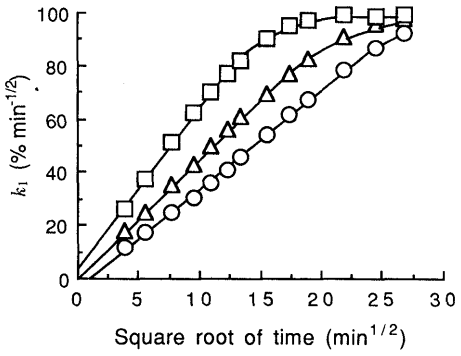

Fig. 1. Release Profiles of PPA as a Function of Square Root of Time from Matrices (Formulation I) Prepared with Different WFHH in SMH-H Filler

○, 90% WFHH; △, 50% WFHH; □, 20% WFHH.

TABLE II. Estimated Values of Release Rates, Constant C and Release Index, Derived from SMH-H Matrix Tablets

WFHH[a] (%)	Eq. 1			Eq. 2			Eq. 4
	k_1[b]	C	r[c]	k_2[b]	n	r[c]	F_{2h}[d]
20	6.332	1.437	0.999	0.0709	0.485	0.999	0.658
33.3	5.807	−4.579	0.996	0.0533	0.479	0.999	0.650
50	4.479	0.584	0.999	0.0479	0.489	0.999	0.645
66.7	4.088	0.794	0.999	0.0399	0.484	0.999	0.642
80	3.920	0.752	0.999	0.0328	0.522	0.999	0.807
90	3.638	−2.280	0.999	0.0276	0.540	0.999	1.161

a) Weight fraction of HPC-H in SMH-H powders. *b*) Release rates, k_1, %min$^{-1/2}$; k_2, min^{-n}. *c*) Linear regression coefficient. *d*) Fraction of drug release due to Fickian mechanism after 2 h of dissolution.

release curve ($M_t/M_\infty < 0.6$) should be used,[11] and thus the upper limit of applicability of Eq. 2 was 60% release. Good linearity was obtained for Eq. 2. In the range of 20—66.7% WFHH, the release exponent was almost the same; however, k_2 decreased with an increase in WFH. On the other hand, when WFHH > 66.7%, the release exponent increased with an increase in WFHH. Since the aspect ratios of these tablets were approximately 1.8, Fickian transport indicates that the release index is 0.43.[12,13] When $n > 0.43$, non-Fickian diffusion behavior is generally observed.[12,13] According to Table II, the release mechanisms from these matrices, therefore, are operated by non-Fickian transport. To evaluate the fraction of drug release due to Fickian mechanisms, the release kinetics of the drug from the matrices was analyzed by application of the equation proposed by Peppas *et al.*,[14] Eq. 3,

$$M_t/M_\infty = f_t/100 = k_3 t^n + k_4 t^{2n} \quad (3)$$

where, k_3 and k_4 express the relative contribution of Fickian and relaxation mechanisms. The relaxational mechanisms involve polymer dissolution and chain disentanglement.[15] The contribution of the diffusional and relaxational mechanism is estimated from the parameters. The fraction of drug release due to the Fickian mechanism, F, was calculated according to Eq. 4,[14]

$$F = 1/(1 + k_4 \cdot t^n/k_3) \quad (4)$$

According to Eq. 4, the value of F varies with time; therefore, in this study F was evaluated after 2 h of dissolution, expressed as F_{2h}, as listed in Table II. At less than 66.7% WFHH of SMH-H, F_{2h} was almost the same, and it can thus be concluded that the contribution of Fickian mechanisms to drug release was the same in the range of 20—66.7% WFHH; however, an increase in WFHH tended to the lower diffusion rate and erosion (or attrition) rate. At more than 66.7% WFHH of SMH-H, as WFHH increased, F_{2h} increased. It was assumed that the contribution of the attrition or erosion was smaller with an increase in WFHH in SMH-H. At 90% WFHH, F_{2h} was greater than unity. It was assumed that diffusion through the gels is a rapid process for PPA and that the matrix would collapse around itself.[16]

Figure 2 shows the relationship between k_1 and WFHH in PMH-H or SMH-H filler. In Fig. 3, k_1 is plotted against the weight fraction of HPC-M (WFHM) in SMH-M or PMH-M filler. In both cases, increases in WFHH and WFHM tended to lower k_1. The relationship between k_1 and WFHM resembled that between k_1 and WFHH; therefore, we studied the effect of WFHH in SMH-H or PMH-H filler on k_1.

k_1 values obtained from various SMH-H matrices were analogous to those from various PMH-H matrices when WFHH was greater than 40%, while k_1 obtained from SMH-H matrix was somewhat greater than that from PMH-H at less than 40% WFHH (Fig. 2). This phenomenon was also observed for the SMH-L matrix. The reason for this is discussed later. The release rate (k_1) from the HPC-H matrix (WFHH was 100%) was smaller than that from the EC matrix (WFHH was zero). It was presumed that in the EC matrix tablets, the drug was released by a leaching action of the medium that entered the EC

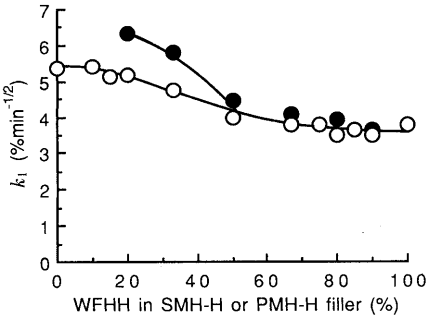

Fig. 2. Influence of WFHH in PMH-H or SMH-H Filler on the Release Rate, k_1, from the Matrix (Formulation I and IV)

○, PMH-H matrix; ●, SMH-H matrix.

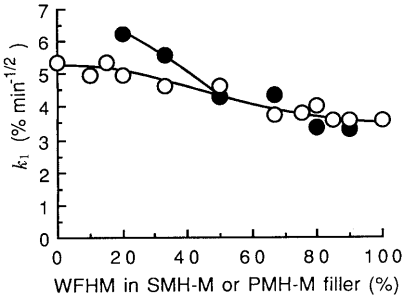

Fig. 3. Influence of WFHM in PMH-M or SMH-M Filler on the Release Rate, k_1, from the Matrix (Formulation II and V)

○, PMH-M matrix; ●, SMH-M matrix.

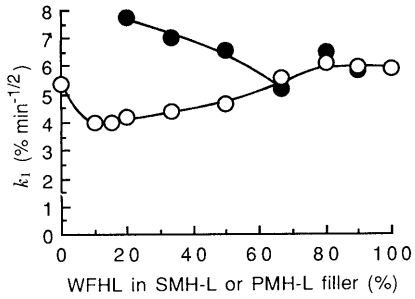

Fig. 4. Influence of WFHL in PMH-L or SMH-L Filler on the Release Rate, k_1, from the Matrix (Formulation III and VI)

○, PMH-L matrix; ●, SMH-L matrix.

matrix through connecting capillaries, while in the HPC-H matrix, the drug release occurred through the capillaries or the gelatinous portion. Thus the release from the HPC-H matrix was delayed due to a retardation of the drug diffusion through the matrix or to the penetration of the medium into the matrix.[17] The addition of HPC-H to the filler tended to decrease k_1. It was therefore assumed that the addition of HPC-H to the EC filler retarded the formation of capillaries because the gels plugged the capillaries. However, the addition of a small amount of HPC-H to the EC polymer, or vice versa, did not affect k_1, and in particular, the k_1 values were almost the same when the WFHH of PMH-H was between 66.7 and 90%.

Figure 4 shows the drug release rate, k_1, plotted against the weight fraction of HPC-L (WFHL) in PMH-L or SMH-L filler. At less than 66.7% WFHL, with increase in WFHL k_1 obtained from the SMH-L matrix increased,

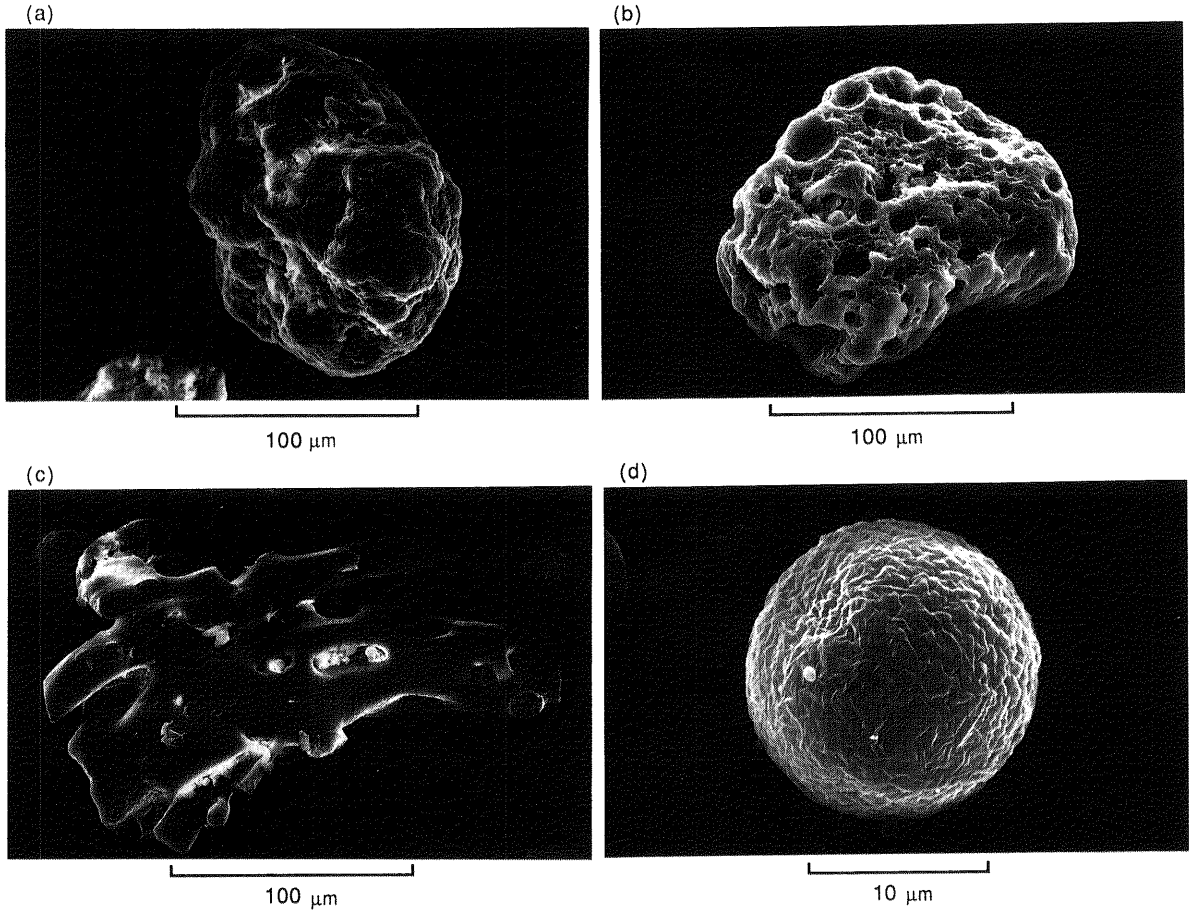

Fig. 5. Scanning Electron Photomicrographs of Commercial EC Product and EC Particles Obtained from Various WFHLs in SMH-L Filler after 6 h Dissolution Test

(a) Commercial product; (b) 33.3% WFHL; (c) 50% WFHL; (d) 80% WFHL.

while that from the PMH-L matrix tended to decrease, except at the point of 0% WFHL. The release rate, k_1, obtained from 10—33.3% WFHL in PMH-L filler was smaller than that from the EC matrix. In particular, the matrices were swollen (an increase in thickness of approximately 11% after a release time of 12 h) at less than 15% WFHL in PMH-L filler, but they did not disintegrate. Therefore, it was assumed that small amounts of HPC-L added to EC acted to delay the diffusion of a drug through the matrix. At more than 50% WFHL in PMH-L filler, increases in WFHL caused the matrix to erode faster, because HPC-L dissolved in water. Therefore, it was considered that an increase in WFHL tended to raise k_1.

On the other hand, in the range of 20—66.7% WFHL in SMH-L filler, the k_1 obtained from the SMH-L matrix increased with a decrease in WFHL, and the k_1 from SMH-L was greater than that from PMH-L, while at more than 66.7% WFHL, the k_1 obtained from the SMH-L matrix was almost the same as that from the PMH-L matrix. This phenomenon might be due to the manufacturing method of the filler. To investigate the cause of accelerated drug release from the SMH-L preparation, photomicroscopic observation was performed.

Figure 5 shows photomicrographs of a commercial EC particle and of EC particles after 6 h of dissolution studies. The commercial EC particle (Fig. 5a) had an irregular shape and no pores. The EC particles containing 20% and 33.3% HPC-L after the 6 h dissolution studies (Fig. 5b) had some large pores, indicating that HPC-L had dissolved out from them. EC particles obtained from 50% or 66.7% SMH-L after 6 h of dissolution studies (Fig. 5c) had various shapes: porous, fiber-like and spherical particles. EC particles obtained from 80% SMH-L after 6 h of dissolution studies (Fig. 5d) were spherical and did not contain any pores. It is assumed that in SMH-L fillers, when WFHL is less than 50%, the HPC-L fraction is dispersed in the EC particles, whereas at greater than 50% WFHL, the EC fraction is dispersed in the HPC-L particles. After dissolving HPC-L, the pores were observed in EC particles at less than 50% WFHL, while the spheres of EC particles were observed at greater than 50% WFHL. In particular, at more than 80% WFHL, all of the EC particles were spherical. It was thought that porous EC particles might promote higher drug release rates because the number of water channels was greater. k_1 values obtained from SMH-L matrices were thus higher than those from PMH-L matrices in the range of 20—50% WFHL. k_1 from the SMH-L matrix became similar to that from the PMH-L matrix at more than 66.7% WFHL. It was considered that at more than 66.7% WFHL, the amount of HPC-L was the governing factor in the filler, and the effect of EC particle shape on k_1 was not determined.

On the other hand, as for the SMH-H and SMH-M

matrices, k_1 from the SMH tablet was greater than that from the PMH tablet at less than 40% WFH. However, the effect of SMH-H and SMH-M at less than 40% WFHH and WFHM on k_1 was small (Figs. 2 and 3). HPC-H and HPC-M formed gels on contact with water and the dissolution rates of HPC-H and HPC-M were very slow. It is presumed that EC particles contained HPC-H or HPC-M fraction in the particles, although the formation rate of the pores for SMH-H and SMH-M is slower than that for SMH-L.

Relationship between Release Rate and Compression Pressure The effect of compression pressure on k_1 is shown in Fig. 6.

As the fillers used had 50% and 80% WFHH, no influence of compression pressure could be detected in this study. The specific gravity of the 80% WFHH matrix at 0.49 MPa was 0.78 g/cm^3, while that at 39.2 MPa was 1.08 g/cm^3. Increases in pressure may alter the tortuosity or porosity of the tablets; however, the drug release rate did not change. Therefore, compression did not modify the properties of the hydrated matrix. This result coincided with a report of Ford *et al.*[18] On the other hand, at 20% WFHL, k_1 increased with a decrease in compression force below 19.6 MPa. It was considered that the attrition of the tablets occurred because of their brittleness during the dissolution test. In this experiment, the specific gravity of all the tablets was calculated from the radius and thickness of the tablet. As the compression pressure was less than 39.2 MPa, the specific gravity of the tablet was less than 1.0 g/cm^3; therefore, the tablets floated in the dissolution medium during the dissolution test. The drug release rates, k_1s, from the tablet were almost equal at various compression pressures, and so this matrix will be used to obtain a floating system in the stomach,[19] which will provide a sustained drug absorption from the gastrointestinal tract.

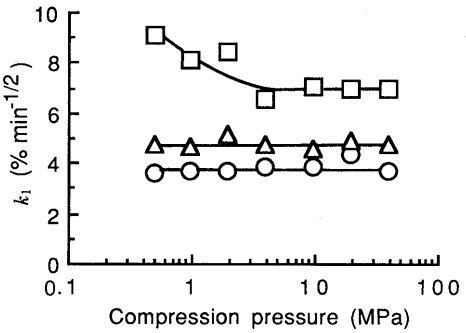

Fig. 6. Influence of Compression Pressure on Release Rate (k_1) from Various WFHHs in SMH-H Fillers

○, 80% WFHH; △, 50% WFHH; □, 20% WFHH.

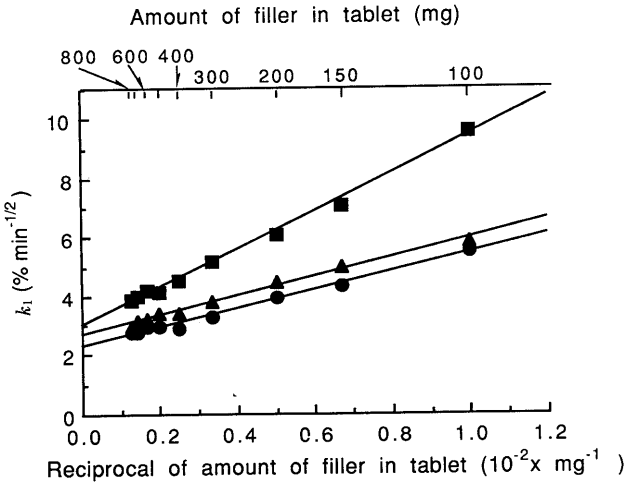

Fig. 7. Relationship between Release Rate (k_1) and Reciprocal Filler Content of Matrix with Constant Amount of PPA

●, 80% WFHH; ▲, 50% WFHH; ■, 20% WFHH.

Relationship between Release Rate and Amount of Filler The effect of PPA dissolution on the amount of the filler which was composed of various WFHHs in SMH-H was investigated. As the amount of filler increased, the k_1 decreased. When the k_1 values were plotted as a function of the reciprocal of the amount of filler, straight lines were obtained, as shown in Fig. 7. In the case of the same amount of filler, k_1 was greater with a decrease in WFHH regardless of the amount of filler. Furthermore, the effect of the amount of filler on k_1 was marked at less than 400 mg of filler, while it was only slight at more than 400 mg of filler in all cases. The general relationship was expressed by the following equation,[20]

$$k_1 = M/W + C \quad (5)$$

where M=slope of derived line (%min$^{-1/2}$·mg), W=weight of filler (mg) and C is constant (%min$^{-1/2}$). The derived values of M and C are given in Table III. The slope of the derived line, M, indicates the degree of effect of the amount of filler on k_1. Theoretically, the value of C represents k_1 at an infinite amount of filler. From the result of the calculated value, C, as WFHH increased, the value of C decreased. Eq. 5 allows the prediction of the tablet composition giving the required dissolution rate of the drug, from previously determined data.

Figure 8 shows the relationship between the initial surface area of the tablet and the release rate (mg·min$^{-1/2}$), k_5. The initial surface area was calculated from the radius

Table III. Derived Values of Slope M and Intercept C

WFHH[a] (%)	Slope M (%min$^{-1/2}$·mg)	Intercept C (%min$^{-1/2}$)	Regression coefficient (r)
20	6.436	2.992	0.998
50	3.302	2.665	0.995
80	3.179	2.282	0.995

a) Weight fraction of HPC-H in filler.

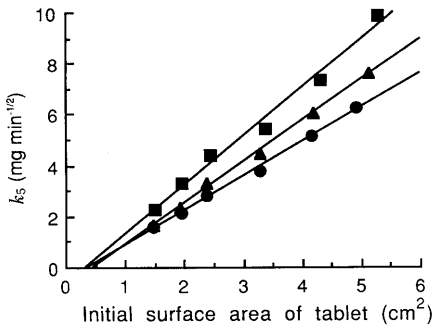

Fig. 8. Relationship between Release Rate (k_5) and Surface Area of Matrix

●, 80% WFHH; ▲, 50% WFHH; ■, 20% WFHH.

and the thickness of the tablet. Direct comparison of the $\%min^{-1/2}$ data was somewhat confusing since the amount of PPA per tablet differed. Therefore, k_5 was expressed as $mg \cdot min^{-1/2}$ in this experiment. A linear relationship was observed between the initial surface area of the tablet and k_5 ($mg \cdot min^{-1/2}$). The regression coefficients of these lines were more than 0.993. The slope of the lines increased with a decrease in WFHH. This indicates that with a lower WFHH, the release rate, k_5, increases. Therefore, if the surface areas of the matrices are the same, k_1 decreases with an increase in WFHH. Figure 2 follows this assumption.

The initial surface area changed with variations in the amount of the matrix by maintaining the PPA: filler ratio and the tablet diameter. A lower initial surface area was associated with a decrease in the thickness of the tablet. When the diameter of the tablet was 7.98 mm, the amount of the matrix approached zero, and the surface area of the tablet might be approximated as unity, the surface area of both (upper and lower) sides. However, the x-intercept was about $0.5\,cm^2$, as shown in Fig. 8. It was thus presumed that as the amount of matrix is approximated to zero, the sides of the tablet become closer to each other and the surface area becomes $0.5\,cm^2$, the surface area of one side.

It was considered that k_5 was related to the surface area of the tablet. This result is in agreement with similar findings of other authors.[18,21] Figure 6 indicates that the compression pressure hardly affected the release rate. The compression pressure may affect the surface area of the tablet, but the surface area ratio at 19.6 to 196 MPa was 1.1 for 20%, 50% and 80% WFHH, so that the effect of compression pressure on the surface area of the tablet was insignificant. Since the surface area of the tablet influenced k_5, the matrix shape, slab, cylinder or sphere might alter k_5. In the case where the dissolution curve of the tablet disintegrating with time did not fit Eq. 1, a good relationship between the surface area of the tablet and k_1 was not found.

Conclusion

It was clarified that with an increase in WFH in the filler, the k_1 from SMH tended to decrease, and the fraction of drug release due to the Fickian mechanism increased when WFHH was greater than 66.7%. The major controlling factors in the drug release rate appeared to be WFH in the filler, HPC viscosity grade and the PPA: filler ratio, while the variation in compression pressure was a minor factor. When HPC-L was used as the filler, release rates were also influenced by the manufacturing method of the filler, namely SMH and PMH. It was assumed that after dissolving HPC-L from WFHL, the porous EC particles might promote drug release because the number of water channels increased. A linear relationship was observed between the release rate and the reciprocal amount of filler, and the surface area of the tablet. According to these relationships, the composition of the tablet can be predicted to obtain the demand release rate of the drug.

Acknowledgment This work was supported in part by a grant from the Human Science Promotion Foundation.

References

1) D. A. Alderman, *Int. J. Pharm. Technol. Prod. Mfr.*, **5**, 1 (1984).
2) M. Nakano, N. Ohmori, A. Ogata, K. Sugimoto, Y. Tobino, R. Iwaoku, K. Juni, *J. Pharm. Sci.*, **72**, 378 (1983).
3) S. K. Baveja, K. V. Rao, K. P. Devi, *Int. J. Pharm.*, **39**, 39 (1987).
4) J. L. Ford, M. H. Rubinstein, F. McCaul, J. E. Hogan, P. J. Edgar, *Int. J. Pharm.*, **40**, 223 (1987).
5) K. V. Rao, K. P. Devi, P. Buri, *J. Controlled Release*, **12**, 133 (1990).
6) S. Aoki, T. Ohwaki, K. Uesugi, K. Tatsuishi, H. Ozawa, M. Kayano, *Int. J. Pharm.*, **85**, 29 (1992).
7) T. Higuchi, *J. Pharm. Sci.*, **52**, 1145 (1963).
8) R. W. Korsmeyer, R. Gurny, E. Doelker, P. Buri, N. A. Peppas, *Int. J. Pharm.*, **15**, 25 (1983).
9) S. Aoki, K. Uesugi, K. Tatsuishi, H. Ozawa, M. Kayano, *Int. J. Pharm.*, **85**, 65 (1992).
10) H. Lapidus, N. G. Lordi, *J. Pharm. Sci.*, **57**, 1292 (1968).
11) N. A. Peppas, *Pharm. Acta Helv.*, **60**, 110 (1985).
12) P. L. Ritger, N. A. Peppas, *J. Controlled Release*, **5**, 23 (1987).
13) P. L. Ritger, N. A. Peppas, *J. Controlled Release*, **5**, 37 (1987).
14) N. A. Peppas, J. J. Sahlin, *Int. J. Pharm.*, **57**, 169 (1989).
15) R. S. Harland, A. Gazzaniga, M. E. Sangalli, P. Colombo, N. A. Peppas, *Pharm. Res.*, **5**, 488 (1988).
16) J. L. Ford, K. Mitchell, P. Rowe, D. J. Armstrong, P. N. C. Elliott, C. Rostron, J. E. Hogan, *Int. J. Pharm.*, **71**, 95 (1991).
17) M. Bamba, F. Puisieux, J. P. Marty, J. T. Carstensen, *Int. J. Pharm.*, **2**, 307 (1979).
18) J. L. Ford, M. H. Rubinstein, J. E. Hogan, *Int. J. Pharm.*, **24**, 327 (1985).
19) P. R. Sheth, J. Tossounian, *Drug Dev. Ind. Pharm.*, **10**, 313 (1984).
20) J. L. Ford, M. H. Rubinstein, J. E. Hogan, *Int. J. Pharm.*, **24**, 339 (1985).
21) J. L. Ford, M. H. Rubinstein, F. McCaul, J. E. Hogan, P. J. Edgar, *Int. J. Pharm.*, **40**, 223 (1987).