Analysis of the Release Process of Phenylpropanolamine Hydrochloride from Ethylcellulose Matrix Granules III.[1] Effects of the Dissolution Condition on the Release Process

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In the pharmaceutical preparation of a controlled release drug, it is very important and necessary to understand the entire release properties. As the first step, the dissolution test under various conditions is selected for the *in vitro* test, and usually the results are analyzed following Drug Approval and Licensing Procedures. In this test, 3 time points for each release ratio, such as 0.2—0.4, 0.4—0.6, and over 0.7, respectively, should be selected in advance. These are analyzed as to whether their values are inside or outside the prescribed aims at each time point. This method is very simple and useful but the details of the release properties can not be clarified or confirmed. The validity of the dissolution test in analysis using a combination of the square-root time law and cube-root law equations to understand all the drug release properties was confirmed by comparing the simulated value with that measured in the previous papers. Dissolution tests under various conditions affecting drug release properties in the human body were then examined, and the results were analyzed by both methods to identify their strengths and weaknesses. Hereafter, the control of pharmaceutical preparation, the manufacturing process, and understanding the drug release properties will be more efficient. It is considered that analysis using the combination of the square-root time law and cube-root law equations is very useful and efficient. The accuracy of predicting drug release properties in the human body was improved and clarified.

Key words ethylcellulose matrix; phenylpropanolamine hydrochloride; square-root time law; cube-root law; simulation; dissolution test

Controlled drug release is a topic of much interest and it is important to understand the properties of drug release and the entire release process.[2] The release properties of the matrix system were mathematically treated by Higuchi,[3] and matrix systems have often been used as a method of controlled drug release. However, it was thought that the mathematical analysis of the release process was insufficient, and the entire release process could not be explained.[1,4] In previous papers, the release process was divided into two stages to understand the entire release process and these were analyzed by the square-root time law and cube-root law equations.[1,4] The validity of the analysis was confirmed by simulating the release process.

In vitro drug dissolution studies are most useful for monitoring drug product stability, manufacturing process control and also predicting the release process in the human body.[5] One method for identifying formulation factors that affect drug bioavailability is the dissolution test,[6] which is very important and necessary to predict the controlled release process. There are many individual practices that differ from person to person. In particular, the status of the human stomach is thought to decide the properties of drug release in the body. Thus, considering the motion and volume of the stomach, the dissolution test was applied, changing some conditions such as volume, rotation speed, pH, and the drug amount.

In this paper, following the Japanese Drug Approval and Licensing Procedures for the dissolution test, release measurements were carried out under various conditions to examine their effects on release properties.[7] Usually, the results are analyzed at any 3 time points with release ratios of 0.2—0.4, 0.4—0.6, and over 0.7, following the guidelines.[7] This method is very simple and useful but it is not able to confirm detailed drug release properties. Accordingly, the results of the dissolution test were analyzed using both methods, *i.e.*, the method following the guidelines and the previously reported analysis method using a combination of the square-root time law and cube-root law equations to examine their practical use. Their validity and utility were subsequently compared and confirmed.

Experimental

Materials The materials described in the previous paper were used.[1,4] Phenylpropanolamine hydrochloride (Powder, Alps Pharmaceutical Ind. Co., Ltd., Gifu, Japan: (PPA)), ethylcellulose 10 cps (ETHOCEL STD 10 cps, DOW Chemical, Tokyo, Japan: (EC)), and ethanol (Wako Pure Chemical Industries, Ltd., Osaka, Japan: (EtOH)) were used.

Equipment The equipment described in the previous paper was used.[1,4] A high shear granulator (High Speed Mixer, LFS-GS-5, volume 5.0 l, Fukae Ind. Co., Ltd., Hyogo, Japan), extrusion granulator (Granulator machine type of LAB, KAR-130, Tsutsui Physics and Chemistry Apparatus Co., Ltd., Tokyo, Japan) were used for granulation. The granules were ground using a speed mill (D-30-4560, Showa Engineering Co., Ltd., Tokyo, Japan).

Preparation of Matrix Granules The formulation for the preparation of matrix granules is shown in Table 1.

Table 1. Formulation for Preparation of Matrix Granules

Formulation	Amount (g)
Composition	
PPA	500
EC	300
EC (in the binder solution)	100
Binder solution	
EC concentration (%)	20
EtOH (%)	90
Volume (ml)	500

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Appropriate amounts of PPA and EC were physically mixed using a high shear granulator for 2 min. They were continually mixed and agitated (agitator 600 rpm, chopper 1500 rpm) by adding drops of binder solution for 5 min. The kneaded mass was then put into the extrusion granulator and granulated with a screen diameter of 1.0 mm and a rotation speed of 20 rpm. The granules were dried overnight at 40—50 °C in a boxtype drying machine. After drying, they were ground using speed mill (screen diameter of 2.0 mm) and sieved. The sieved sample used was 12 mesh pass/18 mesh on granules. The granules obtained are abbreviated as EC matrix granules.

Release Studies Dissolution apparatus (type NTR-VS6P, Toyama Sangyo Co., Ltd., Osaka, Japan) coupled to a flow cell set (type CPS-240B & CPS Controller, Toyama Sangyo Co., Ltd., Osaka, Japan) in a double-beam spectrophotometer (type UV-160A, Shimadzu Co., Ltd., Tokyo, Japan) attached to an auto sampler (type Auto Sampler-W, Toyama Sangyo Co., Ltd., Osaka, Japan) was used.

Release measurements were carried out following the conditions shown in Table 2. The released amount was determined from absorbance measurements at 257 nm.

Results and Discussion

Release Profile The effects of the conditions of the dissolution tests were examined. Release profiles are shown using the release ratio (m_r) in Fig. 1. The release ratio (m_r) is expressed as:

$$m_r = m/M_0 \quad (1)$$

here, M_0 is the initial PPA amount and m is the released amount at time t. They showed similar release curves.

Usually, the release or dissolution result is analyzed by any 3 points such as m_r=0.2—0.4, 0.4—0.6, and over 0.7.[7] So release times were selected as 6, 30 and 90 min and were abbreviated as T_6, T_{30}, and T_{90}, respectively. The results obtained are shown in Table 3. Their values are shown as the permitted release ratio for each point.

This method is very simple but does not clarify the exact evaluation of release properties. The release process should be treated quantitatively as described in the previous paper.[1,4] Following the previously reported method,[1,4] the release process was divided into two stages, and the entire release process was treated by a combination of the square-root time law and cube-root law equations. Hence, the effects of factors on the release properties were evaluated quantitatively.

Application of the Square-Root Time Law and Cube-Root Law Equations The release process could be divided into two stages, and the initial and second stages could be analyzed by the square-root time law and the cube-root law equations, respectively.

Release from the matrix device was analyzed using a semilogarithmic equation at the same time.[8,9] The applicability of the equation to the second stage release process was also examined previously.[1,4] However, it was found that a semilogarithmic equation could not be applied to the treatment in this study because of a lack of correlation with the

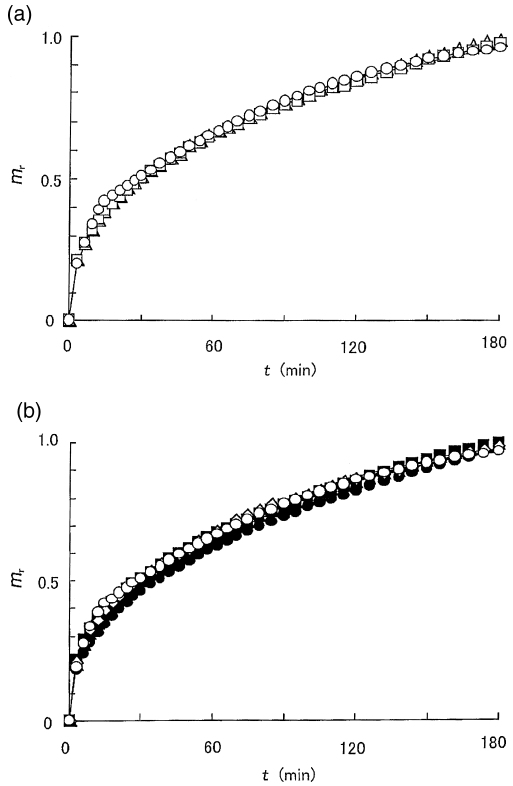

Fig. 1. Release and Simulation Curves of PPA from EC Matrix Granules

(a) ○, F-1; △, F-2; □, F-3. (b) ○, F-1; ◇, F-4; ●, F-5; ▲, F-6; ■, F-7. —, Simulation using the square-root time law and cube-root law equations.

Table 2. Factors of the Dissolution Test at 37 °C

	Factors						
	F-1	F-2	F-3	F-4	F-5	F-6	F-7
Buffer solution volume (ml)	500	500	900	500	500	500	500
pH	1.2	1.2	1.2	4.0	6.5	1.2	1.2
Paddle rotation speed (rpm)	100	100	100	100	100	50	200
EC matrix granule amounts (mg)	250	250	250	250	250	250	250

Table 3. Results of the Release Ratio (%)

Release time (min)	Aim release ratio (%)	Factors						
		F-1	F-2	F-3	F-4	F-5	F-6	F-7
T_6	30±15	27.7	27.3	27.4	28.1	23.9	27.0	28.6
T_{30}	50±15	50.8	49.9	50.6	51.4	46.3	50.4	51.1
T_{90}	75±10	77.7	75.8	76.6	78.0	73.4	76.6	77.4

measured values.

The square-root time law equation[3,10] was expressed as the following equation in terms of the drug release ratio.

$$m_r = K_H\sqrt{t} \quad (2)$$

where K_H is the apparent release rate constant and t is the release time.

The second release process was treated using the cube-root law equation in the same manner as described previously.[1,4]

The cube-root law equation for a single component is expressed as:

$$(M/M_0)^{1/3} = 1-(1/3)kS_{SP}C_S t = 1-K_C t^{11,12)} \quad (3)$$

Here, M ($=M_0-m$) is the undissolved amount remaining in the solution, k is the intrinsic release rate constant, S_{SP} is the specific surface area, C_S is the solubility and K_C is the summarized release rate constant, respectively. As M/M_0 can be rewritten as $1-m_r$, the cube-root law equation for a system of more than two-components is expressed as:

$$(1-m_r)^{1/3} = 1-K_{app}t \quad (4)$$

where K_{app} is the apparent release rate constant.

Following Eqs. 2 and 4, the results obtained with F-1 are shown as an example in Fig. 2. In Fig. 2a, the apparent release rate constant, K_H, was evaluated as the initial slope of the straight line. The estimated K_H value is $0.1125\,\mathrm{min}^{-1/2}$.

In Fig. 2b of the second stage, the obtained straight line was expressed as follows.

$$(1-m_r)^{1/3} = 0.879-0.003001t \quad (5)$$

Hence, the release ratio in the second stage could be simulated using the equation:

$$m_{r,C} = 1-(0.879-0.003001t)^3 \quad (6)$$

where $m_{r,C}$ is the release ratio simulated by the cube-root law equation. Therefore, the second release stage could be well expressed by the generalized equation[1]:

$$(1-m_r)^{1/3} = a-K_{app}t \quad (7)$$

where a is the intersection at the y-axis in the cube-root law plot. The release process might also be simulated as:

$$m_{r,C} = 1-(a-K_{app}t)^3 \quad (8)$$

Release (m_r) and simulation curves ($m_{r,H}$) obtained by using K_H and Eq. 2 are shown in Fig. 3 and they fit well with the measured release curves.[13]

The fit of the simulation curve in the initial stage appeared.

Therefore, the result of these simulations is shown by solid lines in Fig. 1.

Thus, the validity of the analysis method was confirmed as described in the previous paper.[1,4] So it was confirmed that the release process could be divided into two stages, and the entire release process was treated by a combination of the square-root time law and cube-root law equations. The connection point of the square-root time law and cube-root law equations should play an important role to evaluate the entire release process in addition to K_H and K_{app}. The release time and release ratio at the connection point of these simulation curves were expressed by $\sqrt{t_C}$ and m_C, respectively.

In vitro drug dissolution studies are most useful for monitoring drug product stability, control of the pharmaceutical manufacturing process and prediction of the release process in the human body. The movement of the drug product in the stomach is quite different depending on physiologic states such as dehydration, food, physical condition, and so on, and they affect the drug release time and/or the individual difference of release and dissolution in the stomach.

The dissolution test is one method for discriminating formulation factors that affect drug bioavailability.[7] Therefore, the dissolution test under various conditions is very important and necessary for the preparation of a practical controlled release drug.

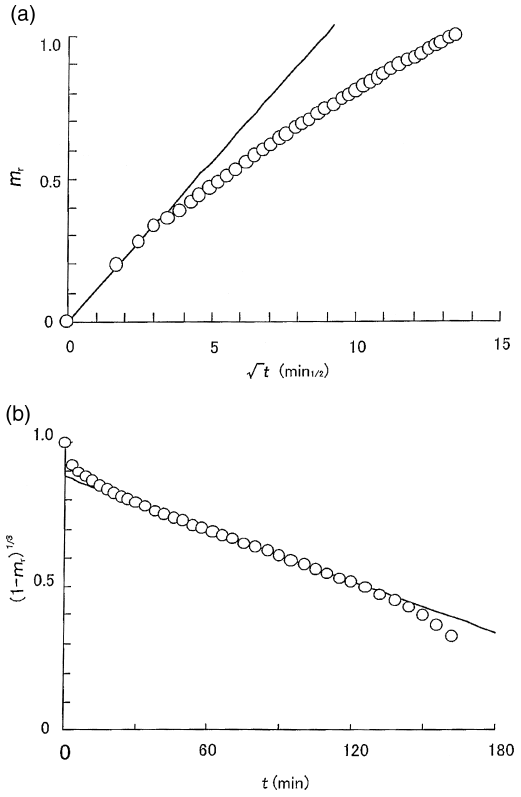

Fig. 2. Analysis of Release Properties for F-1

(a) Square-root time law equation plot. —, Simulation using the square-root time law equation. (b) Cube-root law equation plot. —, Simulation using the cube-root law equation.

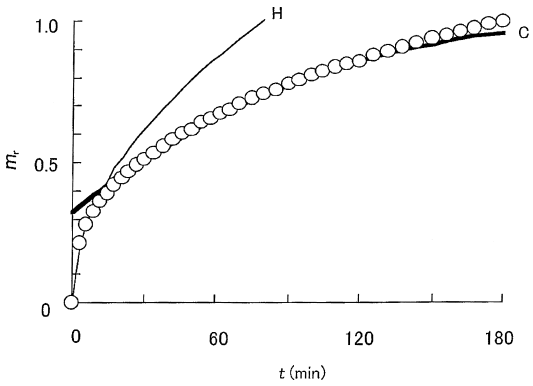

Fig. 3. Release and Simulation Curves for F-1

Curve H, simulation using square-root time law equation; Curve C, simulation using cube-root law equation.

Effect of the Volume of the Buffer Solution on the Re-

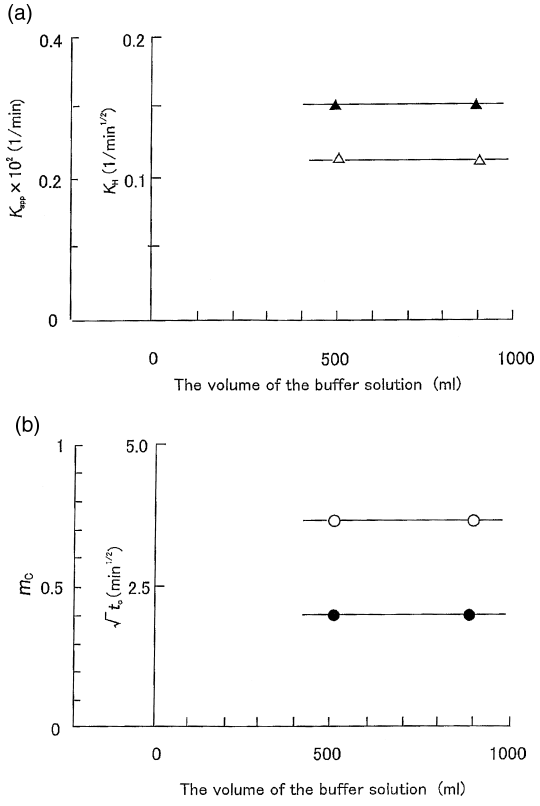

Fig. 4. Effect of the Volume of Buffer Solution

pH=1.2, rpm=100, amount=250 mg. (a) Release rate constant; △, K_H; ▲, K_{app}. (b) Connection point; ○, $\sqrt{t_C}$; ●, m_C.

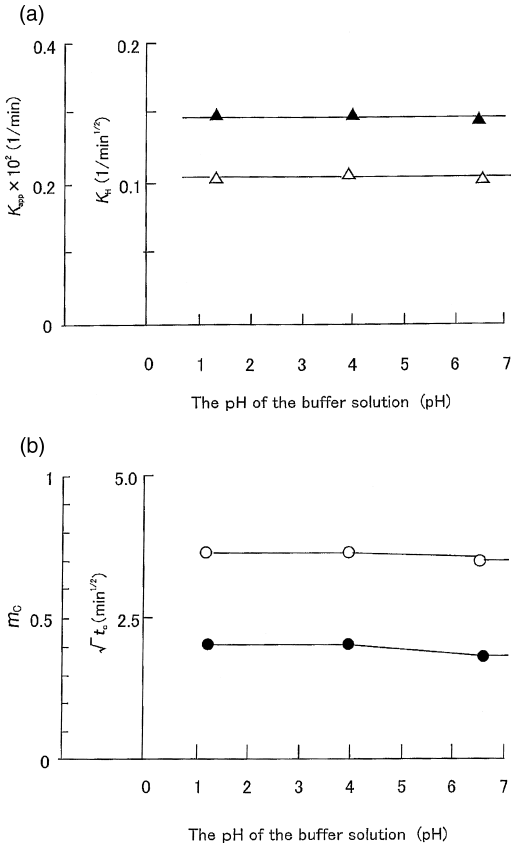

Fig. 5. Effect of the pH of the Buffer Solution

V=500 ml, rpm=100, amount=250 mg. (a) Release rate constant; △, K_H; ▲, K_{app}. (b) Connection point; ○, $\sqrt{t_C}$; ●, m_C.

lease Properties The effect of the volume of the buffer solution on the release properties was examined, using 500 ml (F-1) or 900 ml (F-3) for the dissolution test as a model of the volume of solution in the stomach.[7] The release process was analyzed and simulated by the combination of the square-root time law and cube-root law equations. These are shown by a solid line in Fig. 1a.

Changes in K_H, K_{app}, $\sqrt{t_C}$, and m_C with the volume of the buffer solution were examined, as shown in Fig. 4.

The K_H and K_{app} value showed almost the same value.

The connection point between these equations was considered to play an important role in the release properties. The $\sqrt{t_C}$ and m_C value showed almost the same value.

PPA was released from the gel layer of swollen EC in the matrix granules and K_H is an apparent release rate constant at this stage. As the K_H value shows almost the same, it was considered that the volume of the buffer solution did not affect on the property of gel layer and the drug existing below it. The m_C depends on the character of matrix system. So the m_C value shows constant when the K_H shows the same value.

In the second stage, the drug existing below the gel layer dissolve and was released through the gel layer and an apparent release rate constant K_{app} was obtained in this stage. As the K_{app} showed almost the same value, it was considered that the volume of the buffer solution did not affect on the dissolve and/or release of drug from EC matrix.

Thus it was considered that the release properties of EC matrix granules could not be affected by the volume of the buffer solution in the stomach.

Effect of the pH of the Buffer Solution on the Release Properties Following the guidelines the effect of pH on the release properties was examined, using pH 1.2 (F-1), pH 4.0 (F-4), or pH 6.5 (F-5) buffer solution for the dissolution test as the pH model of the solution in the digestive organs.[7] The release properties were analyzed and simulated by the combination of the square-root time law and cube-root law equations. They are shown by a solid line in Fig. 1b.

Changes in K_H, K_{app}, $\sqrt{t_C}$, and m_C with the pH of the buffer solution were examined, as shown in Fig. 5.

The K_H and K_{app} value of F-1 (pH 1.2) and F-4 (pH 4.0) showed the same value, but F-5 (pH 6.5) was a little smaller than the others.

The $\sqrt{t_C}$ and m_C values of F-1 (pH 1.2) and F-4 (pH 4.0) were almost the same, but F-5 (pH 6.5) was a little smaller than the others.

The release rate of PPA in the pH 6.5 buffer solution was slower than that in the other pH buffer solutions. This might be caused by the pK_a of PPA (pK_a=9.44±0.04), because ethylcellulose is insoluble in water and its release property is less affected by pH,[14,15] but the difference was small and did not cause a significant problem.

Effect of the Paddle Rotation Speed on the Release Properties Considering stomach movement, the effect of the paddle rotation speed on the release properties was examined. Following the guidelines, the effect of the paddle rotation speed on the release properties was examined at 50 rpm (F-6), 100 rpm (F-1), or 200 rpm (F-7) for the dissolution test.[7] The release properties were analyzed and simulated by the combination of the square-root time law and cube-root

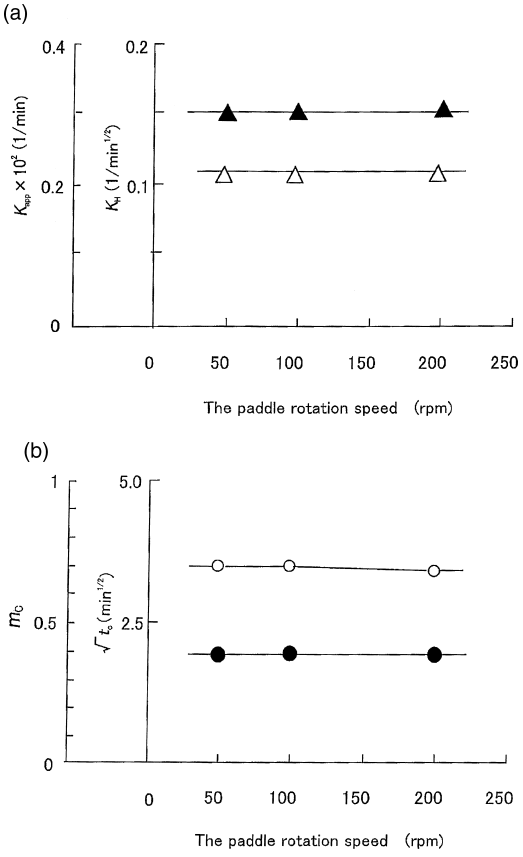

Fig. 6. Effect of Paddle Rotation Speed

V=500 ml, pH=1.2, amount=250 mg. (a) Release rate constant; △, K_H; ▲, K_{app}. (b) Connection point; ○, $\sqrt{t_C}$; ▲, m_C.

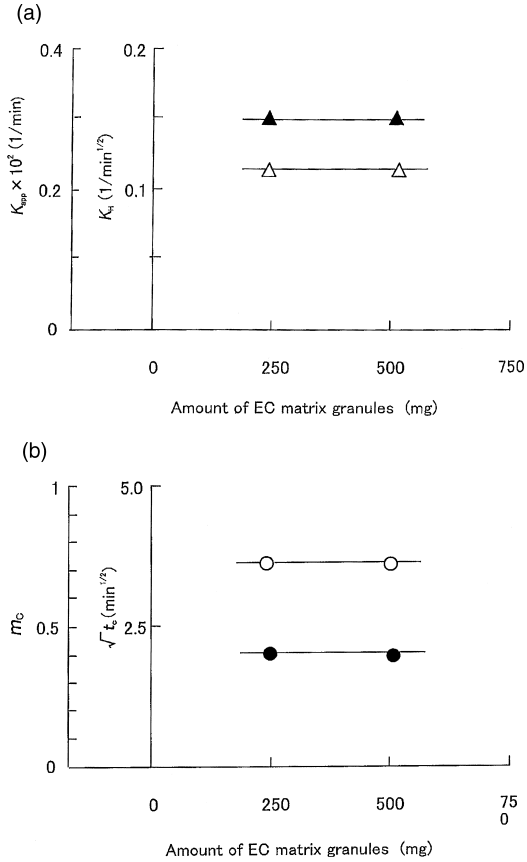

Fig. 7. Effect of the Amount of EC Matrix Granules

V=500 ml, pH=1.2, rpm=100. (a) Release rate constant; △, K_H; ▲, K_{app}. (b) Connection point; ○, $\sqrt{t_C}$; ●, m_C.

law equations. They are shown by a solid line in Fig. 1b.

Changes in K_H, K_{app}, $\sqrt{t_C}$, and m_C with the paddle rotation speed were examined, as shown in Fig. 6.

The K_H and K_{app} values were almost the same. Even if the paddle rotation speed was changed, the $\sqrt{t_C}$ and m_C values showed an almost fixed value.

It was considered that paddle rotation speed did not affect on the drug releases from the gel layer of swollen EC in the matrix granules because of EC is insoluble in water.[14)]

Thus it was considered that the release properties of EC matrix granules could not be affected by the paddle rotation speed within the measured conditions.

Effect of the Amount of EC Matrix Granules on the Release Properties Generally, the dosage is controlled by body weight and/or age; however, the release properties have to be maintained at optimum levels despite changing the dosage. The effect of the amount of EC matrix granules on the release properties was therefore examined. EC matrix granules of 250 mg (containing 139 mg of PPA: F-1) or 500 mg (containing 278 mg of PPA: F-2) were used for the dissolution test under the condition of V=500 ml, pH=1.2 and 100 rpm. The release properties were analyzed and simulated by the combination of the square-root time law and cube-root law equations. Hence their simulation curves are shown by solid lines in Fig. 1a.

Changes in K_H, K_{app}, $\sqrt{t_C}$, and m_C with the amount of EC matrix granules were examined, as shown in Fig. 7.

The K_H and K_{app} values were almost the same, and the amount of EC matrix granules did not affect the $\sqrt{t_C}$ and m_C values.

It was considered that the amount of EC matrix granules did not affect on the drug releases from or through the gel layer of swollen EC in the matrix granules.

It is therefore supposed that the release properties are not affected by the amount of EC matrix granules.

Conclusion

When a controlled release dosage form is produced, its release properties and their affect on bioavailability in the human body should be investigated. The movement of a drug product in the stomach can differ depending on physiologic states such as dehydration, food, and physical conditions. They cause a drug release time difference and/or an individual difference. So release and/or dissolution tests are very important and useful methods for understanding and predicting of the drug release properties. The release test was carried out under various conditions, *i.e.*, the volume of buffer solution, the pH of the buffer solution, paddle rotation speed, and the dosage.

Usually, the measured processes are analyzed following the Japanese Drug Approval and Licensing Procedures. Following this method, the analyzed results showed that the release properties of EC matrix granules could not be affected by these dissolution conditions. Therefore, the measured process was treated using another method, *i.e.*, the combination of the square-root time law and cube-root time law equations.

It was confirmed that the release process could be treated

quantitatively by a combination of the square-root time law and cube-root law equations. It was also considered that this method was appropriate for practical simulations and the prediction of the release process within the measured conditions. The treated results showed that the release properties were less affected by the conditions except the pH condition. They showed very small differences with changes in the pH condition. It was considered that this information is very important and useful for predicting drug release properties in the human body, and it should be used for the better planning of pharmaceutical preparations and understanding details of the release properties.

In pharmaceutical preparation, the dissolution test has to be analyzed using the combination of the square-root time law and cube-root law equations to understanding the details of drug release properties depending on the effect of various conditions. Once its validity has been confirmed, the results could be analyzed following the guideline method. Hereafter, the control of pharmaceutical preparation, and the manufacturing process, and understanding the drug release properties will be more efficient. It is considered that analysis using the combination of the square-root time law and cube-root law equations is very useful and efficient.

In this paper it was examined only about the release property of PPA from EC matrix. So it is necessary that the examination of the release property form the other controlled release system and comparison of *in vitro* with *in vivo* properties. The comparison will be done by analysis of concentration in the blood of beagle dog also.

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