Analysis of the Release Process of Phenylpropanolamine Hydrochloride from Ethylcellulose Matrix Granules IV.[1] Evaluation of the Controlled Release Properties for *in Vivo* and *in Vitro* Release Systems

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In the pharmaceutical preparation of a controlled release drug, it is very important and necessary to understand the release properties. The dissolution test is a very important and useful method for understanding and predicting drug-release properties. It was readily confirmed in the previous paper that the release process could be assessed quantitatively by a combination of the square-root time law and cube-root law equations for ethylcellulose (EC) matrix granules of phenylpropanolamine hydrochloride (PPA). In this paper EC layered granules were used in addition to EC matrix. The relationship between release property and the concentration of PPA in plasma after administration using beagle dogs were examined. Then it was confirmed that the correlativity for EC layered granules and EC matrix were similar each other. Therefore, it was considered that the dissolution test is useful for prediction of changes in concentration of PPA in the blood with time. And it was suggested that EC layered granules were suitable as a controlled release system as well as EC matrix.

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

Controlled drug release is a topic of much interest and it is important to understand the drug release process and properties *in vitro* and *in vivo* for practical application.[2,3] The release properties of the matrix system were mathematically assessed by Higuchi,[4] and matrix systems have often been used as a method of controlled drug release; however, it was considered that the mathematical analysis of the release process was insufficient, because the equation can not explain the entire release process.[1,5,6] In previous papers, the release process was divided into two stages to understand the entire release process and these were analyzed using a combination of the square-root time law and cube-root law equations.[1,5,6] It was concluded that predicting drug release properties using this analysis was useful.

In this paper, the release properties of different controlled release systems, *i.e.*, the physically mixed EC matrix system and EC layered-coating granule system, were examined. Their release process from the different controlled release systems were analyzed using a combination of the square-root time law and cube-root law equations. After evaluating the validity of these equations by comparing the entire simulated release process with the measured one. Bioavailability of PPA from these controlled release systems were examined using beagle dogs.

The relationship between release property and the concentration of PPA in plasma after administration using beagle dogs were examined. Then it was confirmed that the correlativity for EC layered granules and EC matrix were similar each other. Therefore, it was considered that the dissolution test is useful for prediction of changes in concentration of PPA in the blood with time for both systems.

Analyzing the comparison of *in vivo* and *in vitro* measurement, the correlation between the release properties *in vivo* and *in vitro* could be identified. It was considered that the release property of PPA *in vivo* can be predicted by *in vitro* drug dissolution study.[7] Generally EC layered granules might be convenient for the preparation of controlled release dosage forms as compared with EC matrix. And it was suggested that EC layered granules were suitable as a controlled release system as well as EC matrix. Therefore it was suggested that the EC layered granule was useful as well as EC matrix granules.

Experimental

Materials The materials described in the previous paper were used.[1,5,6] Phenylpropanolamine hydrochloride (PPA) (Powder, Alps Pharmaceutical Ind. Co., Ltd., Gifu), ethylcellulose 10 cps (EC) (ETHOCEL STD 10 cps, DOW Chemical, Tokyo), Nonpalel 103 (NP) (Sugar cube, Freund Industrial Co., Ltd., Tokyo), Talc, Polyethylenglycol (PEG), Fe_2O_3 and 90% ethanol (EtOH) (Wako Pure Chemical Industries, Ltd., Osaka) were used.

Equipment The equipment described in the previous paper was used.[1,5,6] A high shear granulator (High Speed Mixer, LFS-GS-5, volume 5.0 l, Fukae Ind. Co., Ltd., Hyogo) and extrusion granulator (Granulator machine type of LAB, KAR-130, Tsutsui Physics and Chemistry Apparatus Co., Ltd., Tokyo) were used for granulation. The matrix granules were ground using a speed mill (D-30-4560, Showa Engineering Co., Ltd., Tokyo), and a high shear granulator was used for layered coating.

Preparation of Dose Capsules Containing Matrix or Layered-Coating Granules The formulation for the preparation of the matrix granules (Granule A) and layered-coating granules (Granule B) are shown in Table 1.

The preparation of Granule A followed the previous paper. 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 box-type drying machine. After drying, they were ground using a speed mill (screen diameter of 2.0 mm) and sieved. The sieved sample was 12 mesh pass/18 mesh for granules. The granules obtained are abbreviated as Granule A.

Granule B was prepared as follows. Appropriate amounts of NP were layered by PPA with binder solution using a high shear granulator under an agitator speed of 200 rpm. They were rotated for 5 min for drying, and the layered-coating EC granules were prepared by using a coating solution of EC. The layered-coating EC granules were dried overnight at 40—50 °C in a box-type drying machine. After drying, the sieved sample was 12 mesh pass/18 mesh for granules. Thus, layered-coating EC granules, *i.e.*, Granule B, was obtained. The preparation process is shown in Fig. 1.

Appropriate amounts of each granule were used for the dose form using #2 capsules, abbreviated as Cap A and Cap B, respectively.

Release Studies Dissolution apparatus (type NTR-VS6P, Toyama

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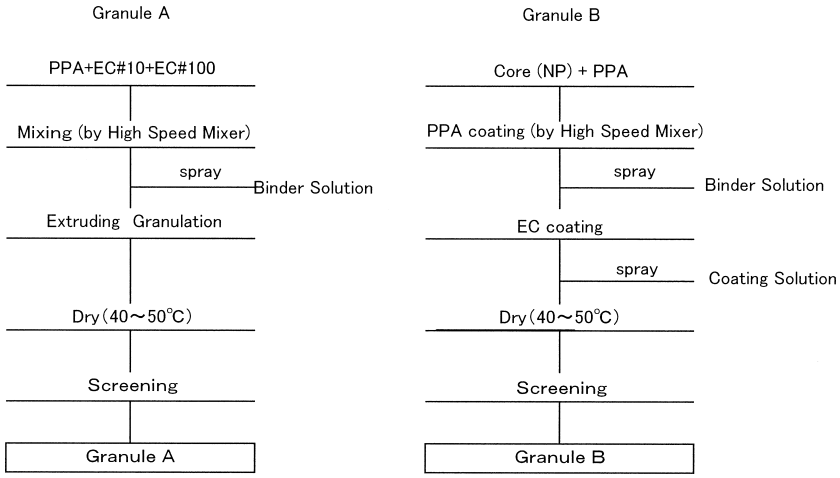

Fig. 1. Flow Chart of Granule Preparation

Table 1. Formulation for Preparation of Dose Capsules

	Granule A	Granule B
Composition (amount: g)		
PPA	500	500
EC#10	300	
NP103		750
Binder Solution		
EC concentration (%)	20	7
EC#10 (g)	100	35
Volume (ml)	500	500
Coating Solution		
EC concentration (%)		7.00
Talc concentration (%)		1.00
PEG concentration (%)		1.00
EtOH concentration (%)		90.99
Fe_2O_3 concentration (%)		0.01
EC#10 (g)		83.55
Volume (ml)		1193.50
for dose #2 capsules	Capsule A	Capsule B
Granule (mg)	108	116.97
PPA /cap (mg)	60	60
EC/cap (mg)	48	9.96

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

Cap A or Cap B was put into the dissolution apparatus, and the release measurement was carried out with 500 ml of buffer solution (first solution pH 1.2) at a paddle rotation speed of 100 rpm at 37 °C. The released amount was evaluated from absorbance measurements at 257 nm.

Estimation of Bioavailability of EC Matrix Granules and EC Layered-Coating Granules The bioavailability test was carried out under the crossover method. Cap A or Cap B was administrated with 10 ml water to 6 female beagle dogs (6 months old) fasted for 24 h. Bioavailability was examined by analysis of blood concentration following the method shown in Fig. 2. Blood (6 ml) was sampled at 8 points (pre, 1, 2, 3, 4, 6, 8, 12 h) after administration. The plasma sample was obtained by adding heparin to the blood sample. The amount of PPA extracted from plasma was analyzed using the HPLC method.

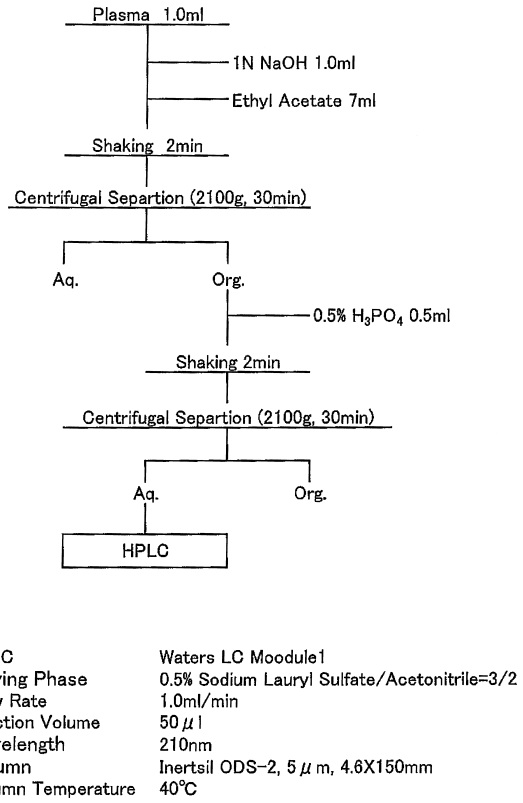

Fig. 2. Method of PPA Extraction from Pasma

Results and Discussion

Release Profile (*in Vitro*) The dissolution test was examined.

The release profile is shown using the release ratio (m_r) in Fig. 3.

The release ratio (m_r) is expressed as:

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

where M_0 is the initial PPA amount and m is the released PPA amount at time t. Cap A and Cap B showed similar release curves.

The release process should be treated quantitatively to obtain clear release properties as described in the previous paper.[1,5,6] Following the previously reported method,[1,5,6] the release process was divided into two stages. At the initial stage, PPA was released from the gel layer of swollen EC in the granules. At the second stage, the drug existing below the

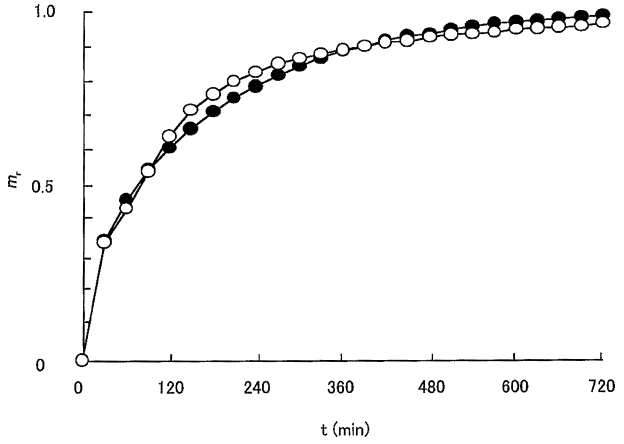

Fig. 3. Release of PPA from Capsule A and B
●, Capsule A; ○, Capsule B.

gel layer dissolved, and was released through the gel layer. 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.

Analysis of Entire Release Process The release processes of Cap A and Cap B were analyzed together using a semilogarithmic equation.[8,9] The applicability of the equation to the second stage release process was also examined previously,[1,5,6] however, it was found that the semilogarithmic equation could not be applicable to treatment for these release studies because of a lack of correlation with the measured values. The release process was the divided into two stages and the initial and second stages were analyzed by the square-root time law and cube-root law equations, respectively.

The square-root time law equation[4,10] was expressed as the following equation in terms of the drug-release ratio.

$$m_r = K_H\sqrt{t} \tag{2}$$

where K_H is the apparent release rate constant and t is the release time. But the entire release process could not be analyzed. Therefore the second release process was treated using the cube-root law equation in the same manner as described previously.[1,5,6]

The cube-root law equation for a single component is expressed as[11,12]:

$$(M/M_0)^{1/3} = 1-(1/3)kS_{SP}C_St = 1-K_Ct \tag{3}$$

where, 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:

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

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

Following Eqs. 2 and 4, the results obtained are shown in Fig. 4.

In Fig. 4a, the apparent release rate constant, K_H, was evaluated as the initial slope of the straight line. The estimated K_H values of Cap A and Cap B were $0.061\,\mathrm{min}^{-1/2}$ and

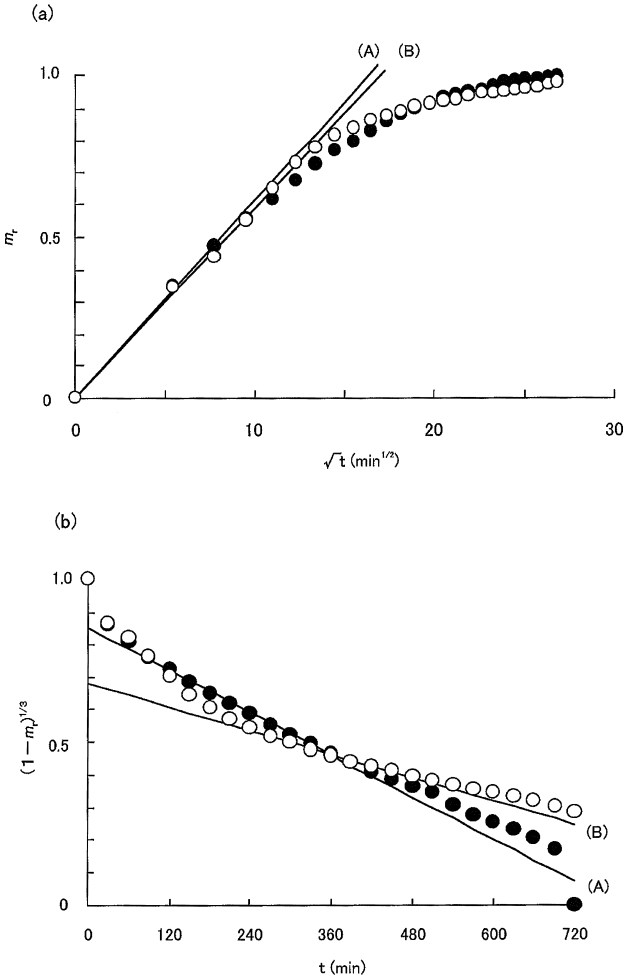

Fig. 4. (a) Analysis of Release Properties by the Square-Root Time Law Equation
●, Capsule A; ○, Capsule B. —, simulation using the square-root time law equation.
(b) Analysis of Release Properties by the Cube-Root Law Equation
●, Capsule A; ○, Capsule B. —, simulation using the cube-root law equation.

$0.059\,\mathrm{min}^{-1/2}$, respectively. The K_H values were almost the same. It was considered that their release properties were similar in the initial stage. The initial stage was a water channel forming process, and PPA was released from the gel layer of swollen EC.

In Fig. 4b of the second stage, the obtained straight line of Cap A as an example was expressed as follows.

$$(1-m_r)^{1/3} = 0.85399-0.001089t \tag{5}$$

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

$$m_{r,C} = 1-(0.85399-0.001089t)^3 \tag{6}$$

where $m_{r,C}$ is the release ratio simulated by the cube-root law equation. The simulated values are shown in the Figure, and a fairly good relationship was obtained; therefore, the second release stage could be well expressed by the generalized equation[6]:

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

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

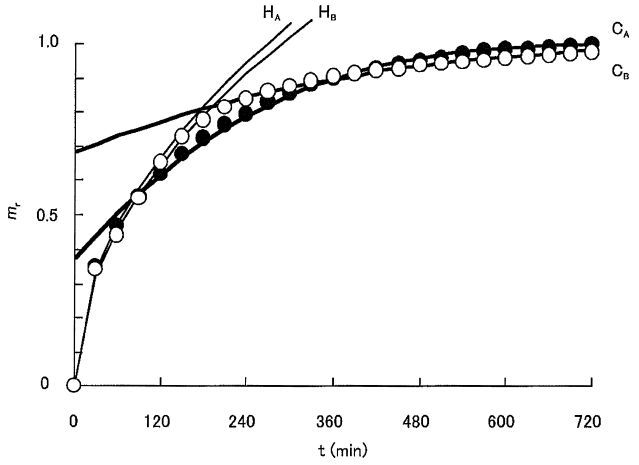

Fig. 5. Release and Simulation Curves

●, Capsule A; ○, Capsule B. Curve H_A, simulation using the square-root time law equation for Capsule A; Curve H_B, Simulation using the square-root time law equation for Capsule B; curve C_A, simulation using the cube-root law equation for Capsule A; curve C_B, simulation using the cube-root law equation for Capsule B.

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

The estimated K_{app} values of Cap A and Cap B were $0.0011\,min^{-1}$ and $0.0006\,min^{-1}$, respectively.

Release and simulation curves obtained by using K_H, K_{app}, Eq. 2, and Eq. 8 are shown in Fig. 5.

Simulation curves fit well with the measured release curves.[13] The fit of the simulation curve appeared in the initial stage; thus, the validity of the analysis method for Cap A and Cap B was confirmed as expected from the previous paper.[1,5,6] It was therefore 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, irrespective of dose preparation, *i.e.*, Cap A and Cap B.

The connection point of the square-root time law and cube-root law equations should play an important role in evaluating 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. The values of $\sqrt{t_C}$ and m_C were $9.06\,min^{1/2}$, 0.554 for Cap A, and $13.93\,min^{1/2}$, 0.822 for Cap B, respectively. $\sqrt{t_C}$ is the length of time of initial stage, and $\sqrt{t_C}$ of Cap A was shorter than Cap B. *i.e.*, the water channel forming process in the EC layered granules took time longer than in the EC matrix.

Bioavailability Bioavailability of PPA from capsules was examined by analysis of the PPA concentration from the blood of beagle dogs. The change of the PPA concentration in plasma with time is shown in Fig. 6.

The values of *AUC*, C_{max} and T_{max} were 5.1479 mg/ml h, 0.7767 mg/ml and 3 h for Cap A, and 4.9775 mg/ml h, 0.7172 mg/ml and 3 h for Cap B, respectively. They showed similar curves, but the standard error in the data of Cap A was larger than Cap B. It was considered that the release property of Cap B *in vivo* was more stable than Cap A.

Correlation between Release Properties and Bioavailability The correlation between the concentration of PPA in plasma and the released amount or release ratio are shown in Fig. 7. The *x*-axis shows released amount or released ratio of PPA instead of the release time in Fig. 6.

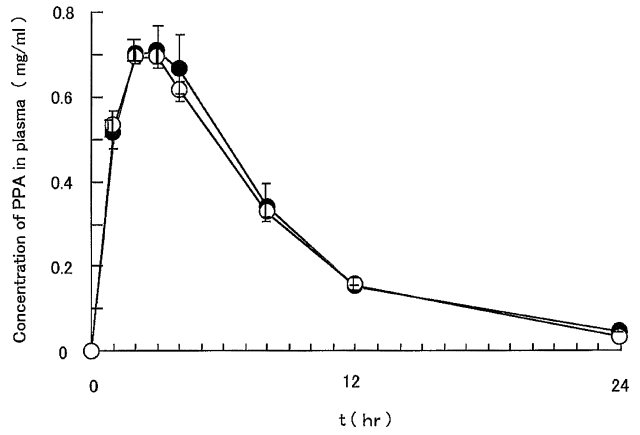

Fig. 6. Concentration of PPA in the Blood of Beagle Dogs

●, Capsule A; ○, Capsule B.

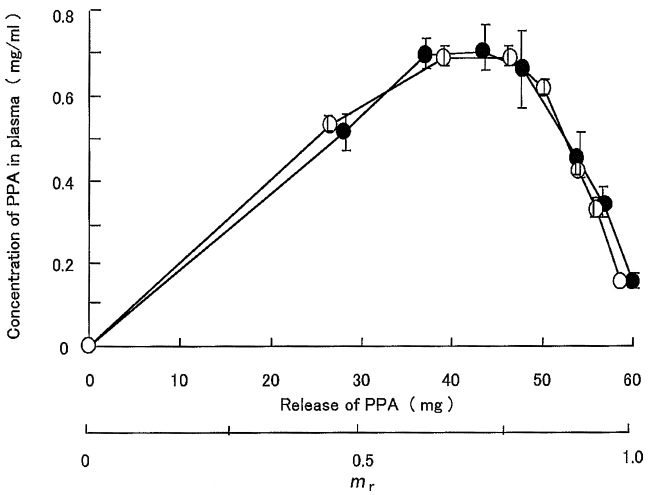

Fig. 7. Correlation between Release Properties and Bioavailability

●, Capsule A; ○, Capsule B.

They showed very similar curves, but the standard error in the data of Cap B was little. Hence, it was considered that bioavailability of Cap B was less affected by individual practices that differ from person to person.

Here, the C_{max} appears where the release ratio of PPA (m_r) is about 0.75, as. therefore the value of C_{max} can be predicted from a dissolution test when the dose is confirmed.

Properties of Cap A and Cap B Release properties of Cap A and Cap B were examined *in vitro* and *in vivo* Cap A and Cap B contained EC matrix granules and EC layered-coating granules, respectively. The K_H value showed a similar value in Cap A and Cap B but their K_{app} value showed a little different. At the initial stage, PPA was released from the gel layer of swollen EC in the matrix and layered granules. In the first stage, it was considered that they had similar release properties. In the second stage, PPA below the gel layer dissolved, and was released through the gel layer; therefore, it was considered that characteristic release properties might appear in the second release stage.

Cap A and Cap B were examined for bioavailability using beagle dogs. The analyzed result was quite similar, so it was considered that the bioavailability of Cap A and Cap B has

similar properties. Comparing the dose preparation, it is easier to control the manufacturing process of EC layered-coating granules than EC matrix granules. So it was considered that Cap B is more convenient than Cap A concerning the preparation and practical use.

Conclusion

When a controlled release dosage form is produced, its release properties and their effect on bioavailability in the human body should be investigated, and release and/or dissolution tests are very important and useful for understanding and predicting drug-release properties. When release and/or dissolution tests are carried out, the release process should be treated quantitatively. A combination of the square-root time law and cube-root law equations was confirmed to be a useful equation for qualitative treatment. It was also considered that this method was applicable for practical simulations and the prediction of the release process within the measured conditions.

Here, the dissolution and the bioavailability of PPA using beagle dogs was examined for Cap A and Cap B. The release properties of PPA from the capsules showed very similar. So it was confirmed that it is possible to predict and understand bioavailability by the dissolution test. In this case, the C_{max} apperes where the release ratio of PPA (m_r) is about 0.75, as. Therefore the value of C_{max} can be predicted when the dose is confirmed.

Comparing the dose preparation, it is easier to control the manufacturing process of EC layered-coating granules than EC matrix granules. So it was considered that Cap B is more convenient than Cap A. It was confirmed that further investigation with EC layered-coating granules will bring practical and useful results.

References and Notes

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