Analysis of the Release Process of Phenylpropanolamine Hydrochloride from Ethylcellulose Matrix Granules

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The release properties of phenylpropanolamine hydrochloride (PPA) from ethylcellulose (EC, ethylcellulose 10 cps (EC#10) and/or 100 cps (EC#100)) matrix granules prepared by the extrusion granulation method were examined. The release process could be divided into two parts, and was well analyzed by applying square-root time law and cube root law equations, respectively. The validity of the treatments was confirmed by the fitness of the simulation curve with the measured curve. At the initial stage, PPA was released from the gel layer of swollen EC in the matrix granules. At the second stage, the drug existing below the gel layer dissolved, and was released through the gel layer. Also, the time and release ratio at the connection point of the simulation curves was examined to determine the validity of the analysis. Comparing the release properties of PPA from the two types of EC matrix granules, EC#100 showed more effective sustained release than EC#10. On the other hand, changes in the release property of the EC#10 matrix granule were relatively more clear than that of the EC#100 matrix granule. Thus, it was supposed that EC#10 is more available for controlled and sustained release formulations than EC#100.

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

The control of drug release is a topic of much interest. It is important to grasp the entire release process to control drug release.[1] Release properties of the matrix system were mathematically treated by Higuchi; the matrix system has often been used as a method to control drug release. As the matrix forms, granule, tablet,[2—5] film coating[6—8] and so on are available,[9—12] and the matrix system was often prepared by the use of a polymer.[13,14] However, it has been thought that mathematical analysis of the release process is insufficient, and that the entire release process is not obvious.

It was supposed that the release process would be easy to manipulate, because ethylcellulose (EC) is insoluble in water, and its release property is less affected by pH.[15,16] In this paper, EC was used as a polymer matrix substance, and the matrix granule was prepared by the extrusion granulation method. Then, the release of phenylpropanolamin hydrochloride (PPA) as a model drug from the matrix granule was carried out. The release process was analyzed by means of a square-root time law equation, and the validity of the treatment was examined by comparing the simulated value with the measured value. According to the square-root time law equation, the drug release continues infinitely even though the content of drug in the matrix granule decreases gradually. Since the release process deviated that expected from the equation, semi-logarithmic and cube root law equations were examined to analyze the entire release process, in addition to the square-root time law equation. After evaluating the validity of these equations by comparing the simulated entire release process with the measured one, the effects of EC content of different molecular weight[17] on the release process were examined.

Experimental

Materials Phenylpropanolamine hydrochloride (Powder, Alps Pharmaceutical Ind. Co., Ltd., Gifu: abbreviated as PPA), ethylcellulose 10 cps (ETHOCEL STD 10 cps, DOW Chemical, Tokyo: abbreviated as EC#10), ethylcellulose 100 cps (ETHOCEL STD 100 cps, DOW Chemical, Tokyo: abbreviated as EC#100) and ethanol (Wako Pure Chemical Industries, Ltd., Osaka: abbreviated as EtOH) were used.

Equipment High shear granulator (High Speed Mixer, LFS-GS-5, volume 5.0 l, Fukae Ind. Co., Ltd., Hyogo), extrusion granulator (Granulator machine type of LAB, KAR-130, Tsutsui Physics and Chemistry Apparatus Co., Ltd., Tokyo) and speed mill (D-30-4560, Showa Engineering Co., Ltd., Tokyo) were used.

Preparation of Matrix Granules Formulations are shown in Tables 1 and 2. A binder solution of 20% EC was prepared with 90% EtOH.

Following the formulation, a proper amount of PPA and EC#10 or EC#100 were physically mixed using the high shear granulator for 1 min. It was continually mixed by adding drops of the binder solution (total 500 ml) as it was mixed and agitated (agitator 600 rpm, chopper 1500 rpm) for 5 min. Then, the kneaded mass was put into the extrusion granulator and granulated under the conditions of a screen diameter of 1.0 mm and a rotation speed of 20 rpm. Next, the granules were dried overnight at 40—50 °C in a box type drying machine. After drying, they were ground by a 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 were abbreviated as EC#10 matrix granule and EC#100 matrix granule, respectively.

Release Studies A dissolution apparatus (type NTR-VS6P, Toyama Sangyo Co., Ltd., Osaka) coupled to a flow cell set (type CPS-240B & CPS

Table 1. Formulations

Ingredients	Formulation						
	F-1	F-2	F-3	F-4	F-5	F-6	F-7
	Amounts (mg)						
PPA	500	500	500	500	500	500	500
EC#10	200	300	400	900			
EC#100					200	300	400

Table 2. Formulations of Binder Solution in 500 ml

Ingredients	Formulation						
	F-1	F-2	F-3	F-4	F-5	F-6	F-7
	Amounts (g)						
EC#10	100	100	100	100	—	—	—
EC#100	—	—	—	—	100	100	100

Using 90% EtOH.

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Controller, Toyama Sangyo Co., Ltd., Osaka) in a double beam spectrophotometer (type UV-160A, Shimadzu Co., Ltd., Tokyo) attached with an auto sampler (type Auto Sampler-W, Toyama Sangyo Co., Ltd., Osaka) was used.

Granules of 500 mg were put into the 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 determined from the absorbance at 257 nm.

Results and Discussion

Release Profile Release profiles are shown using the release ratio (m_r) in Fig. 1.

It was observed that the drug release rate decreased with an increase in EC content. Release processes for all formulations were analyzed. However, the results obtained with the F-3 formulation are shown below as an example.

Applicability of Square-Root Time Law Equation The release ratio is expressed by Eq. 1.

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

here, m is the released amount and M_0 is the initial amount.

Hence, the square-root time law equation[18,19] can be expressed as Eq. 2 by use 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. Following Eq. 2, the m_r *versus* $\sqrt{t}$ plot was shown in Fig. 2.

The apparent release rate constant, K_H, was evaluated as the slope of the straight line, and the release ratio could be simulated by using K_H and Eq. 2 ($m_{r,H}$).

Release and simulation curves are shown in Fig. 3.[20]

The fitness of the simulation curve at the initial stage was confirmed, but the entire release process could not be analyzed. As described, it is important to grasp the entire release process to control drug release. Therefore, the release process was divided into two parts and analyzed.

Applicability of Cube Root Law Equation Sometimes, release from the matrix device was analyzed by the use of a semi-logarithmic law equation.[13,14] The applicability of this equation to the second stage release process was examined. However, it was considered that a semi-logarithmic law equation could not be applied to the treatment of the present study because of less correlation with measured values. Therefore, treatment of the second release process by means of a cube root law equation was examined.

The cube root law equation for a single component was expressed by Eq. 3.[21,22]

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

Here, M ($=M_0-m$) is the amount remaining in the solution, k is the 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 is equal to $1-m_r$, the cube root law equation for more than a two-component system was expressed as:

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

where K_{app} is the apparent release rate constant. Following Eq. 9, the analyzed result is shown in Fig. 4 as an example.

A straight line, expressed as follows, was obtained.

$$(1-m_r)^{1/3} = 0.9071-0.00407t \quad (5)$$

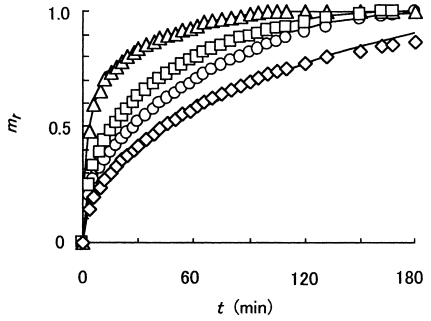

Fig. 1. Release and Simulation Curves of PPA from Matrix Granules

△, F-1; □, F-2; ○, F-3; ◇, F-4. —, Simulation using square-root time law and cube root law equations.

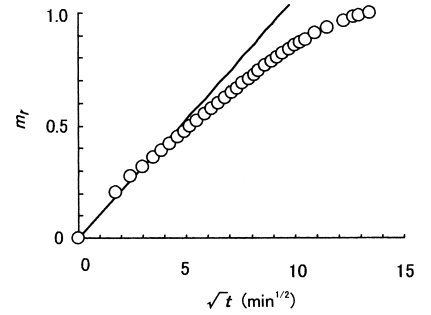

Fig. 2. Square Root-Time Law Equation Plot for F-3

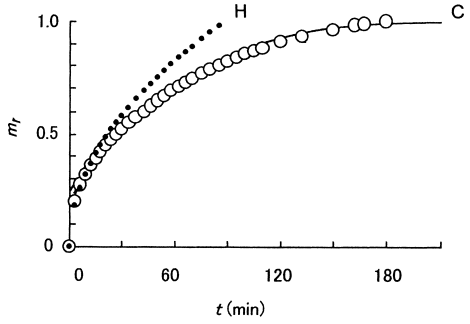

Fig. 3. Release and Simulation Curves for F-3

H, $m_{r,H}$; C, $m_{r,C}$.

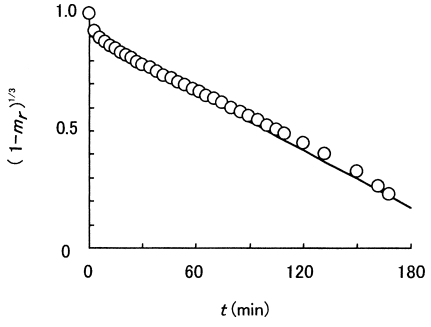

Fig. 4. Cube Root Law Equation Plot for F-3

Hence, the release ratio at the second stage was simulated by using the equation:

$$m_{r,C} = 1-(0.9071-0.00407t)^3 \quad (6)$$

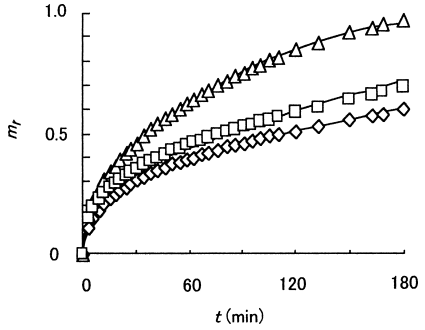

Fig. 5. Release and Simulation Curves of PPA from Matrix Granules
△, F-5; □, F-6; ◇, F-7. —, Simulation using square-root time law and cube root law equations.

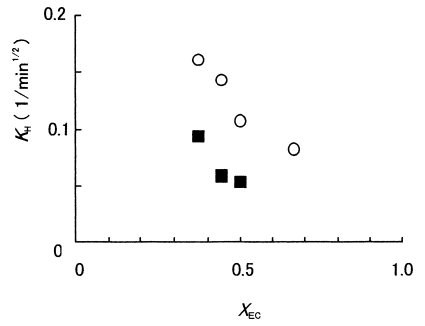

Fig. 6. Relationship between K_H and X_{EC}
○, EC#10; ■, EC#100.

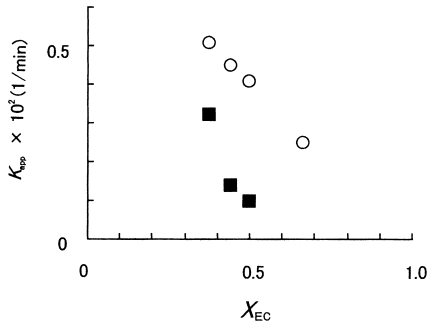

Fig. 7. Relationship between K_{app} and X_{EC}
○, EC#10; ■, EC#100.

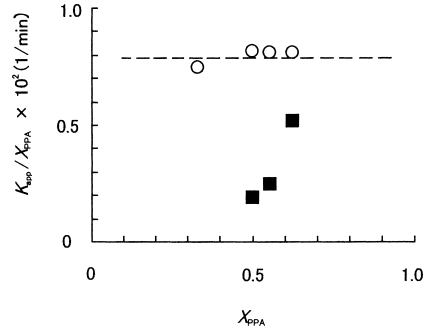

Fig. 8. Relationship between K_{app}/X_{PPA} and X_{PPA}
○, EC#10; ■, EC#100.

where $m_{r,C}$ is the release ratio simulated by the cube root law equation. The simulated release ratio is shown in Fig. 4 by a solid line. At the second release stage, the simulated values fit well with those measured. In analysis of the release from the other formulation, the same form equation expressed by Eq. 10 was obtained, and gave satisfactory simulation values for each formulation. Therefore, it was considered that the second release stage could be well expressed by the generalized equation:

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

where a is the intersect at the Y-axis in the cube root law plot. The release process might be expressed as:

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

Thus, it was considered that the release process was divided into two stages, and the initial and second stages could be explained by square-root time law and cube root law equations, respectively. At the initial stage, PPA was released from the gel layer of swollen EC in the matrix granule. At the second stage, PPA existing below the gel layer dissolved, and was released through the gel layer.

In the same manner, the release and simulated curves for EC#100 matrix granules are shown in Fig. 5.

Changes in K_H with Content of EC K_H is an apparent release rate constant at the first release stage obtained by applying the square-root time law equation. The relationship between the mixed weight fraction of EC (X_{EC}) and K_H is shown in Fig. 6.

The K_H value decreased with an increased X_{EC} value. This might be caused by the swelling and gel formation property of EC. EC is water insoluble, and the thickness and formation time of the gel layer depends on X_{EC}. So, the release of PPA from EC matrix granules was delayed with an increased EC content ratio. Comparing the K_H values, the values obtained from EC#10 matrix granules were larger than those obtained from EC#100 matrix granules. It was supposed that the larger the molecular weight of polymer, the more swelling and viscose the binder solution. So, these properties of the binder solution were thought to play an important role in the release process.

Changes in K_C or K_{app} with the Content of EC K_{app} is an apparent dissolution rate at the second release stage obtained by applying the cube root law equation. The relationship between the mixed weight fraction of EC (X_{EC}) and K_{app} is shown in Fig. 7.

The K_{app} value decreased with an increase in the X_{EC} value. Considering that the available drug content for dissolution or release changes in accordance with the content of PPA, the effect of the mixed weight fraction of PPA (X_{PPA}) on K_{app} was examined, and expressed as K_{app}/X_{PPA}. Hence, the relationship between K_{app}/X_{PPA} and X_{PPA} was shown in Fig. 8.

The K_{app}/X_{PPA} value was relatively close when the binder solution of EC#10 was used. Hence, Eq. 7 could be roughly expressed as:

$$(1-m_r)^{1/3}=a-xK_Ct \tag{7}'$$

On the other hand, the K_{app}/X_{PPA} value decreased with increasing X_{EC} when the binder solution of EC#100 was used. The difference might arise from the difference in the structure of matrix due to the swelling property. It was considered that the process of release from granules prepared using EC#10 is more understandable, and therefore more useful to

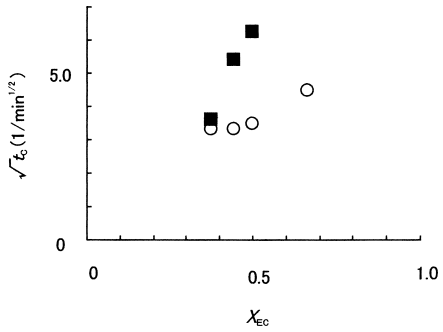

Fig. 9. Relationship between $\sqrt{t_C}$ and X_{EC}
○, EC#10; ■, EC#100.

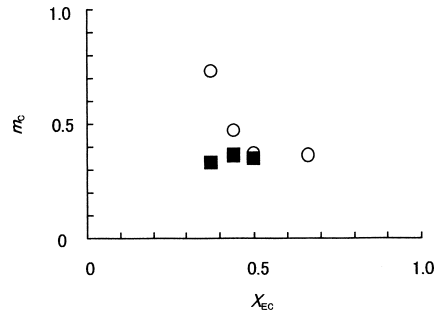

Fig. 10. Relationship between m_C and X_{EC}
○, EC#10; ■, EC#100.

predict or control release.

Connection Point of the First and Second Release Processes The release process can be simulated by using square-root time law and cube root law equations. It was considered that the connection point of these equations played important role in the analysis of the release process. The time and release ratios at the connection point of these simulation curves were expressed as $\sqrt{t_C}$ and m_C, respectively.

Changes in $\sqrt{t_C}$ and m_C with X_{EC} were examined, as shown in Figs. 9 and 10.

As the EC content ratio increased, $\sqrt{t_C}$ increased. In other words, as the EC content ratio increased, the time of compatibility with the square-root time law equation increased. The EC content ratio influenced the swelling process of EC. And as the EC content ratio increased, m_C decreased. This expressed that the release of PPA was controlled and affected by EC content. However, a clear relationship between them could not be obtained here, even though the connection points expressed as $\sqrt{t_C}$ and m_C were thought to play an important role in the prediction of the release process and/or the preparation of a controlled release formulation.

Conclusion

The release properties of PPA from matrix granules prepared by the extrusion granulation method were examined. EC#10 or EC#100 was used in the preparation of granules for the purpose of controlled release. The release process could be divided into two stages, which were treated by a combination of square-root time law and cube root law equations.

Applicability or validity of the treatment was examined by simulation of the release process.

The initial stage was a water channel forming process, and drug was released at the same time. As the value of the release rate constant (K_H) in the first stage decreased with an increasing EC content ratio and molecular weight of EC, it was considered that the swelling property might be taken into account, in addition to EC content.

Since the second release stage could be analyzed by a cube root law equation, the property of the matrix layer was almost fixed there. The value of the release rate constant (K_{app}) in the second stage decreased with an increase in EC content ratio and/or a decrease in PPA content ratio (X_{PPA}). Taking into account the available drug content, changes in K_{app}/X_{PPA} were examined. The K_{app}/X_{PPA} value was almost constant in the case of the EC#10 matrix granule, while it decreased with increasing EC and decreasing PPA content in the case of the EC#100 matrix granule. Hence, the release property of the EC#10 matrix granule was more comprehensible, compared with that of EC#100 matrix granule. It was thus considered that EC#10 might be useful for the preparation of controlled release dosage forms.

The time (t_C) and relative released amount (m_C) at the intersection where the release stage changes from the first to the second, were examined in terms of EC or drug content.

Increasing the EC content ratio, t_C increased and the m_C of the EC#10 matrix granule decreased, while that of EC#100 matrix granule remained almost constant. However, obvious regulation between them could not be obtained at the present time.

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