Analysis of the Release Process of Phenylpropanolamine Hydrochloride from Ethylcellulose Matrix Granules II.[1] Effects of the Binder Solution on the Release Process

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The release properties of phenylpropanolamine hydrochloride (PPA) from ethylcellulose (EC) matrix granules prepared by an extrusion granulation method were examined. The release process could be divided into two parts; the first and second stages were analyzed by applying square-root time law and cube-root law equations, respectively. The validity of the treatments was confirmed by the fitness of a simulation curve with the measured curve. In the first stage, PPA was released from the gel layer of swollen EC in the matrix granules. In the second stage, the drug existing below the gel layer dissolved and was released through the gel layer. The effect of the binder solution on the release from EC matrix granules was also examined. The binder solutions were prepared from various EC and ethanol (EtOH) concentrations. The media changed from a good solvent to a poor solvent with decreasing EtOH concentration. The matrix structure changed from loose to compact with increasing EC concentration. The preferable EtOH concentration region was observed when the release process was easily predictable. The time and release ratio at the connection point of the simulation curves were also examined to determine the validity of the analysis.

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

The control of drug release is a topic of much interest. The matrix system has often been used as a method to control drug release. Granules, tablets,[2—5] film coatings,[6—8] *etc.* are available,[9—12] and the matrix system is often prepared with the use of a polymer.[13,14] It is important to understand the entire release process to control drug release.[15,16] The release properties of the matrix system were mathematically simulated by Higuchi.[17] According to the square-root time law equation, drug release continues infinitely even though the content of drug in the matrix granules decreases gradually. Therefore it has been thought that the mathematical analysis of the release process is insufficient, and the entire release process is not easily understood.

In a previous paper, ethylcellulose (EC) was used as a polymer matrix substance and the release of phenylpropanolamine hydrochloride (PPA) as a water-soluble model drug from matrix granules prepared by an extruding granulation method was investigated.[1] The release process could be divided into two parts, and the entire release process was treated by a combination of the square-root time law and cube-root law equations. The validity of the mathematical treatment was examined by comparing the simulated value with the measured value. Then effects of EC content ratio and its molecular weight[18] on the release process were examined.[1] The connection point of these equations played an important role in the analysis of the release process. It was confirmed that EC 10 cps might be useful for the preparation of controlled-release dosage forms.

In this paper, the EC matrix granules were prepared using a binder solution of a different composition. The release process was analyzed using a combination of square-root time law and cube-root law equations.[1] After evaluating the validity of these equations by comparing the entire simulated release process with the measured one, the effects of the formulation of the binder solution on the release process were examined.

Experimental

Materials PPA (powder, Alps Pharmaceutical Industries Co., Ltd., Gifu, Japan), EC 10 cps (ETHOCEL STD 10 cps, Dow Chemical, Tokyo, Japan), and ethanol (EtOH) (Wako Pure Chemical Industries, Ltd., Osaka, Japan) were used.

Equipment A high-shear granulator (High Speed Mixer, LFS-GS-5, volume 5.0 l, Fukae Ind. Co., Ltd., Hyogo, Japan) and 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 with speed mill (D-30-4560, Showa Engineering Co., Ltd., Tokyo, Japan).

Preparation of Matrix Granules Formulations are shown in Table 1. While maintaining the content of EC constant, a binder solution of 20% or 30% EC was prepared with 80% to 100% EtOH.

Following the formulation, 500 g of PPA and 300 g of EC were physically mixed using a high-shear granulator for 1 min. The mixture was continually mixed and agitated (agitator 600 rpm, chopper 1500 rpm) by adding drops of the binder solution for 5 min. Then the kneaded mass was placed in the extrusion granulator and granulated with a screen diameter of 1.0 mm and a rotation speed of 20 rpm. Then the granules were dried overnight at 40—50 °C in a box-type drying machine. After drying, they were ground with 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 are abbreviated as EC matrix granules.

Release Studies A 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 with an auto sampler (Auto Sampler-W, Toyama Sangyo Co., Ltd.) 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 amount released was determined based on absorbance measurements at 257 nm.

Results and Discussion

Release Profile The effects of EtOH and EC content in the binder solution were examined. Release profiles are shown using the release ratio (m_r) in Fig. 1. The release ratio (m_r) is given by Eq. 1.

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

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Table 1. Formulations and Binder Solution

	Formulation				
	B-1	B-2	B-3	B-4	B-5
Composition			Amount (g)		
PPA			500		
EC			300		
EC (in the binder solution)			100		
Binder solution					
EC concentration (%)	20	20	20	20	30
EtOH (%)	100	90	85	80	90
Volume (ml)	500	500	500	500	333.3

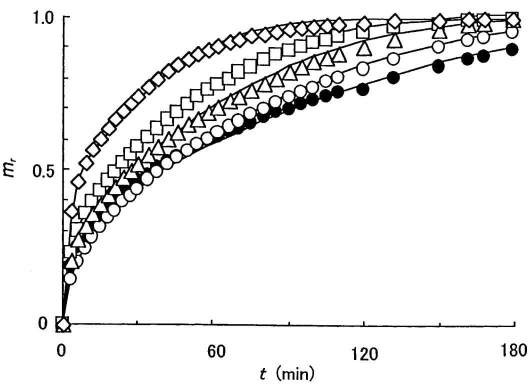

Fig. 1. Release and Simulation Curves of PPA from EC Matrix Granules

○, B-1; △, B-2; □, B-3; ◇, B-4; ●, B-5. —, Simulation using square-root time law and cube-root law equations.

where M_0 is the initial amount and m is the released amount at time t.

It was observed that the drug release rate increased with the decrease in EtOH and/or EC content in the binder solution.

Applicability of Square-Root Time Law Equation The square-root time law equation[17,19] was expressed as Eq. 2 using the drug release ratio.

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

where K_H is the apparent release rate constant and t is the release time. Following Eq. 2, the influence of EtOH or EC content in the binder solution is shown in Figs. 2a and b, respectively.

The apparent release rate constant K_H was evaluated as the slope of the initial straight line. The K_H value decreased with increasing EtOH content in the binder solution. However, the K_H value was constant irrespective of EC content in 90% EtOH binder solution. Release (m_r) and simulation curves ($m_{r,H}$) are obtained using K_H and Eq. 2 ($m_{r,H}$) and are shown in Fig. 3 as an example.[20]

The fit of the simulation curve at the first stage was confirmed, but the entire release process could not be analyzed.[1] As described previously, it is important to understand the entire release process to control drug release. Therefore the release process was divided into two parts and then analyzed.

Applicability of the Cube-Root Law Equation In the same cases, release from the matrix device was analyzed by the use of a semilogarithmic law equation.[13,14] The applicability of the equation to the second-stage release process was

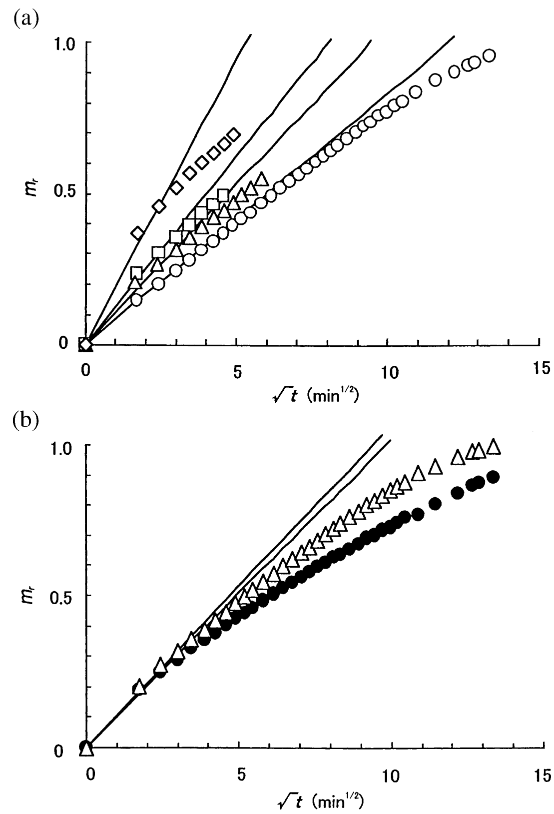

Fig. 2. Square-Root Time Law Equation Plot

(a) ○, B-1; △, B-2; □, B-3; ◇, B-4. (b) EtOH concentration: 90%. △, B-2; ●, B-5.

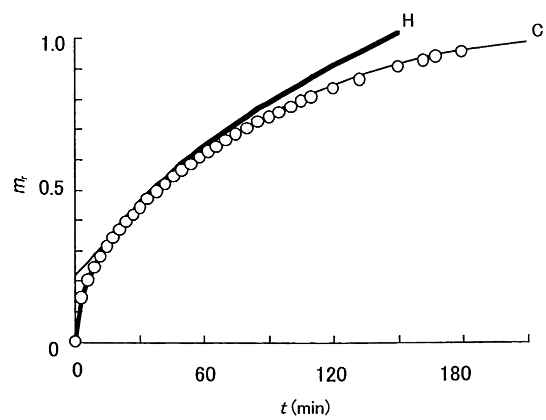

Fig. 3. Release and Simulation Curves for B-1

○, B-1; H, simulation using square-root time law equation; C, simulation using cube-root law equation.

also examined. However, it was found that a semilogarithmic law equation could not be applied to the treatment of the present study because of the lack of correlation with measured values. Therefore the second release process was treated using a cube-root law equation in the same way as previously.[1)]

The cube-root law equation for a single component is expressed by Eq. 3.[16,21)]

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

Were M $(=M_0-m)$ is the undissolved 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. As M/M_0 can be rewritten as $1-m_r$, the cube-root law equation for a system with 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 Eq. 4, the influence of EtOH or EC content in the binder solution is shown in Figs. 4a and b, respectively.

A straight line, expressed as follows, was obtained with the B-1 formulation as an example.

$$(1-m_r)^{1/3}=0.9218-0.00324t \quad (5)$$

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

$$m_{r,C}=1-(0.9218-0.00324t)^3 \quad (6)$$

where $m_{r,C}$ is the release ratio simulated by the cube-root law equation, shown in Fig. 4. In the second release stage, these simulated values fit well with measured values. In the analysis of the release from the other formulation shown in Figs. 5 and 6, the same form of equation expressed by Eq. 5 was obtained and gave satisfactory simulation values for each formulation. 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 y-axis intersection in the cube-root law plot. The release process might also be expressed as:

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

Thus the release process could be divided into two stages, and the first and second stages could be explained by the square-root time law and cube-root law equations, respectively. Therefore the result of these simulations is shown by solid lines in Fig. 1.

Relationship between K_H and Water Content K_H is an apparent release rate constant at the first release stage obtained by applying the square-root time law equation. The validity of the K_H values was confirmed by the simulation. The effects of the EtOH and EC content in the binder solution were examined. The relationship between the water or EtOH content in the binder solution and K_H is shown in Fig. 5a.

The K_H value decreased with increasing EtOH content in the binder solution. The K_H values remained irrespective of EC contents in the binder solution measured. As EC is an EtOH-soluble substance, the amount of EC dissolved in the binder solution depends on the EtOH content, and consequently increases with increasing EtOH content. When a fixed amount of EC was used, the ratio of the concentration against solubility was low and homogeneous, and the volume of the solution increased with increasing EtOH content. When the EtOH content was fixed, homogeneity may hold at first and decrease gradually with increasing EC content. Therefore the binding process in the granulation of prepared matrix granules should be affected by the EtOH content. Thus water and/or EtOH content in the binder solution is an important factor for the formation of a uniform matrix.

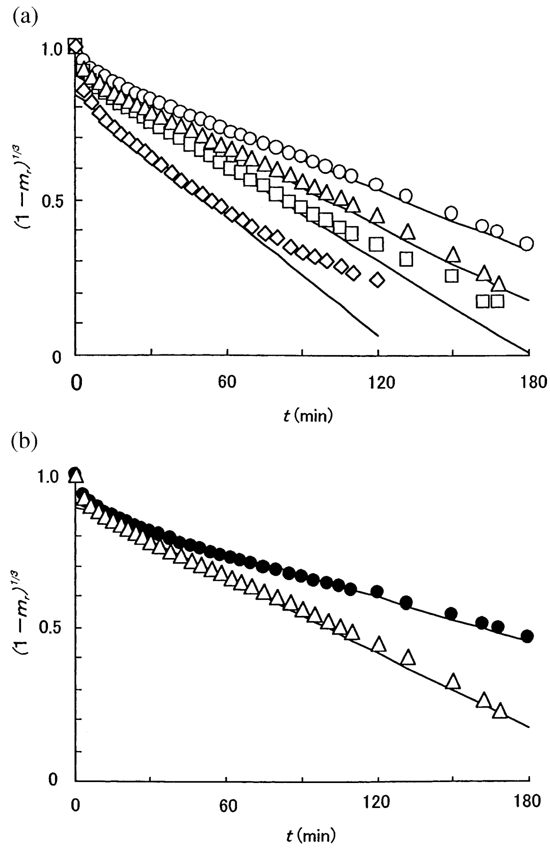

Fig. 4. Cube-Root Law Equation Plot
(a) ○, B-1; △, B-2; □, B-3; ◇, B-4. (b) △, B-2; ●, B-5.

As previously described, the K_H value decreased with the increase in the mixed weight fraction of EC.[1)] Here it was shown that the K_H value could be controlled by adjusting the EtOH content in the binder solution when the mixed weight fraction of EC was constant.

Relationship between K_{app} and Water Content K_{app} is an apparent dissolution rate constant in the second release stage obtained by applying the cube-root law equation. The relationship between the water or EtOH content in the binder solution and K_{app} is shown in Fig. 5b.

The K_{app} value increases with increasing water content in the binder solution. The K_{app} value decreased with increasing EC content when the binder solution prepared with 90% EtOH concentration was used.

In this examination, the release of PPA from EC matrix could be controlled by increasing the EtOH and/or EC content. It was thought that the matrix structure became smoother with increasing EtOH and/or EC content in the binder solution.

The solubility of EC increased with increasing EtOH content in the binder solution. The fluidity of the solution pre-

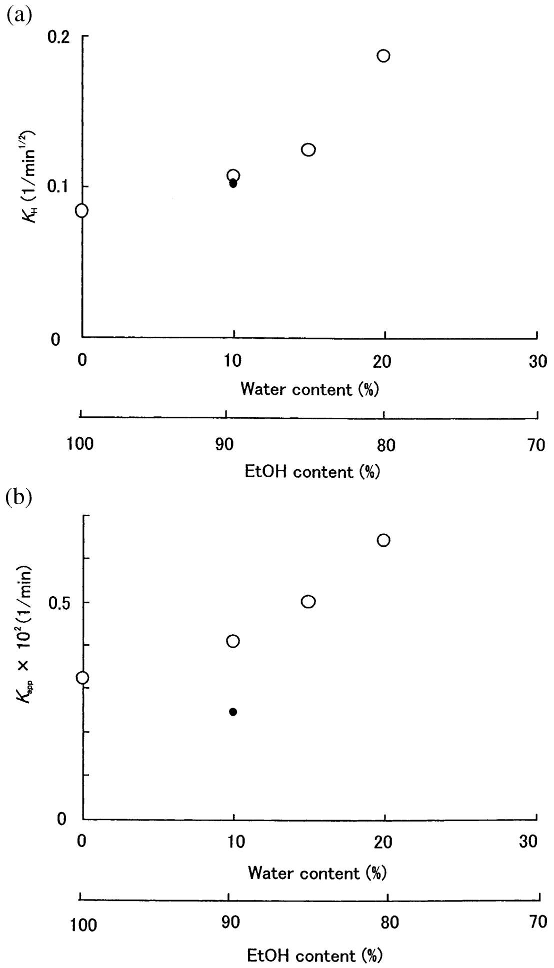

Fig. 5. Relationship between (a) K_H and Water Content and (b) K_{app} and Water Content in the Binder Solution

EC content and volume of the binder solution: ○, EC 20%, 500 ml; ●, EC 30%, 333.3 ml.

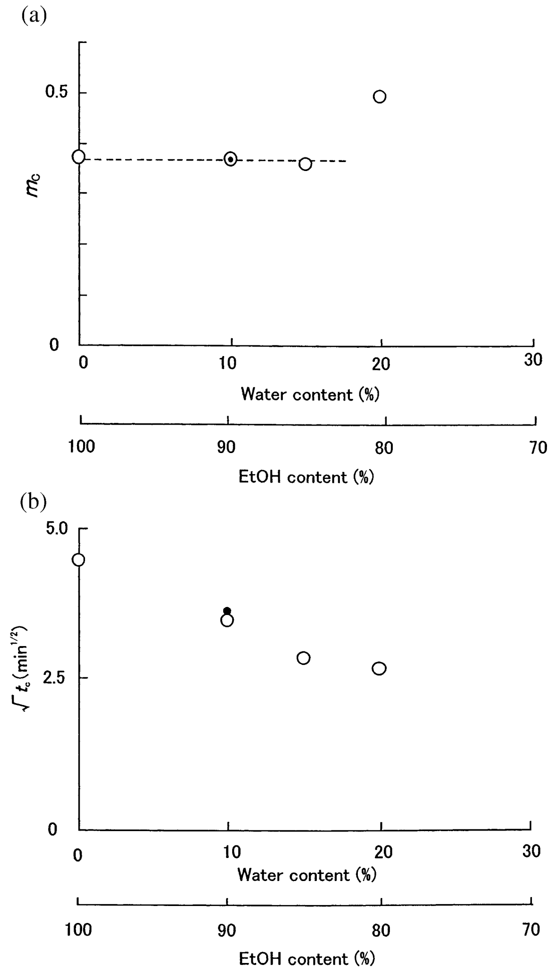

Fig. 6. Relationship between (a) m_C and Water Content and (b) $\sqrt{t_C}$ and Water Content in the Binder Solution

EC content and volume of the binder solution: ○, EC 20%, 500 ml; ●, EC 30%, 333.3 ml.

pared with a fixed amount of EC increased with increasing EtOH content in the binder solution. Conversely, the fluidity of the solution decreased with increasing EC content in the binder solution. Therefore the matrix structure could be affected by the EtOH and EC content in the binder solution.

Connection Point of the First and Second Release Stage The release process can be simulated using the square-root time law and cube-root law equations. The connection point between these equations plays an important role in the analysis of the entire release process. The release time and release ratio 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 the water or EtOH content in the binder solution were examined and shown in Figs. 6a and b.

The m_C value was nearly constant (0.364) when the water content was less than around 15% in the binder solution. In other words, the m_C value remained almost constant when the EtOH concentration was larger than 85%. Hence it was considered that the prediction and comprehension of the control of the amount released was easy in this range. It was also considered that an EtOH concentration of more than 85% had to be used for a satisfactory binder solution.

The $\sqrt{t_C}$ value decreased with increasing water content in the binder solution. However, despite changes in EC content in the 90% EtOH binder solution, $\sqrt{t_C}$ had a nearly constant value. Overall, m_C showed an almost constant value in this region, and it was assumed that the binder solution prepared in this region results in predictable analysis conditions.

Conclusion

The release properties of PPA from matrix granules prepared by the extrusion granulation method were examined. EC was used in the preparation of granules for the purpose of controlled release. The release process could be divided into two stages. The first and second stages were treated using square-root time law and cube-root law equations, respectively. Using the release rate constants in the first stage (K_H) and the second stage (K_{app}), the applicability and validity of the mathematical treatment were examined by simulation of the release process. It was suggested that the release of PPA from matrix granules was affected by the EtOH content in the binder solution, as well as the mixed weight fraction, as reported previously.[1]

The K_H and K_{app} values decreased with increasing EtOH content in the binder solution. The K_H value showed almost the same value and the K_{app} value decreased with increasing EC content in 90% EtOH binder solution. The solubility of EC increased with increasing EtOH content in the binder solution. The fluidity of the solution prepared with a fixed amount of EC increased with increasing EtOH content in the binder solution. Conversely, the fluidity of the solution decreased with increasing EC content in the binder solution. Therefore the matrix structure was affected by the EtOH and EC content in the binder solution.

The release ratio and time at the connection point of the two stages were expressed as m_C and $\sqrt{t_C}$, respectively. The $\sqrt{t_C}$ value increased with increasing EtOH content in the binder solution, whereas the $\sqrt{t_C}$ value remained almost the same with increasing EC content in the 90% EtOH binder solution. The m_C value was almost constant when the EtOH content in the binder solution was greater than 85%.

It was believed that the connection point was fixed in this region and that the entire release process could be analyzed by square-root time law and cube-root law equations. Therefore the prediction and comprehension of the control of amounts released were simple in this region.

References

1) Fukui A., Fujii R., Yonezawa Y., Sunada H., *Chem. Pharm. Bull.*, **50**, 1439—1444 (2002).
2) Shaikh N. A., Block L. H., Abidi S. E., *Drug Dev. Ind. Pharm.*, **13**, 2495—2518 (1987).
3) Pather S. I., Russel I., Syce J. A., Neau S. H., *Int. J. Pharmaceut.*, **164**, 1—10 (1998).
4) Aoki S., Ohwaki T., Uesugi K., Tatsuishi K., Ozawa H., Kayano M., *Int. J. Pharmaceut.*, **85**, 29—38 (1992).
5) Abd EI-Gawad A. H., Gabr K., Said Y. E., *Pharm. Ind.*, **55**, 83—86 (1993).
6) Boles M. G., Deasy P. B., Donnellan M. F., *J. Microencapsul.*, **11**, 55—67 (1994).
7) Takei N., Unosawa K., Matsumoto S., *J. Soc. Powder Technol.*, **36**, 98—105 (1999).
8) Tang L., Wigent R. J., Schwartz J. B., *Pharm. Dev. Technol.*, **4**, 481—490 (1999).
9) Zhaopeng H., Kimura G., Mawatari S., Shimokawa T., Yoshikawa Y., Takada K., *J. Controlled Release*, **56**, 293—302 (1998).
10) Diarra M., Muster D., *Biomaterials*, **19**, 1523—1527 (1998).
11) Ichikawa H., Fukumori Y., *J. Controlled Release*, **63**, 107—119 (2000).
12) Tamura N., *Powder Sci. Engi.*, **32**, 37—43 (2000).
13) Guojie X., Sunada H., *Chem. Pharm. Bull.*, **43**, 483—487 (1995).
14) Guojie X., Ruhuna Z., Wei C., Sunada H., *J. Chin. Pharm. Sci.*, **9**, 26—30 (2000).
15) Yonezawa Y., Ishida S., Sunada H., *Chem. Pharm. Bull.*, **49**, 1448—1451 (2001).
16) Sunada H., Shinohara I., Otsuka A., Yonezawa Y., *Chem. Pharm. Bull.*, **37**, 1889—1894 (1989).
17) Higuchi T., *J. Soc. Cosmetic Chemists*, **11**, 85—97 (1960).
18) Yuasa H., Ozeki T., Kanaya Y., Ohishi K., *Chem. Pharm. Bull.*, **41**, 933—936 (1993).
19) Higuchi T., *J. Pharm. Sci.*, **52**, 1145—1149 (1963).
20) Higuchi T., *J. Pharm. Sci.*, **50**, 874—875 (1961).
21) Hixson A. W., Crowell J. H., *Ind. Eng. Chem.*, **23**, 923—931 (1931).