Development of a Novel Drug Release System, Time-Controlled Explosion System (TES). III.¹ Relation between Lag Time and Membrane Thickness

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To describe lag time of Time-Controlled Explosion System (TES), the system’s water absorption kinetics was investigated. Study of water absorption in TES with EC membrane revealed the following relations: (i) the square of water-uptake linearly increased with time in accordance with the Washburn equation, (ii) the water permeation rate correlated with the reciprocal of membrane thickness, (iii) the amount of water-uptake necessary for membrane destruction was directly proportional to the thickness of the membrane. These results suggest that lag time of TES is regulated by the function of membrane thickness. Indeed, the observed lag time was confirmed to fit with the curve expected by the above relations. When talc was included in the EC membrane in an equal weight ratio as a membrane-filler, lag time related directly to the membrane thickness. Compared with TES consisting of EC membrane only, the membrane was destroyed by a smaller amount of uptake water owing to the weakening of membrane strength by the talc addition.

Keywords time-controlled explosion system (TES); lag time; membrane thickness; membrane destruction; water-uptake; membrane-filler

A novel controlled drug release system called Time-Controlled Explosion System (TES) has been developed. This system basically consists of four laminar layers from center to outside, i.e., core, drug, swelling agent and water insoluble polymer membrane in this order.¹,² The structure possessing a swelling agent layer differentiates TES from the conventional membrane controlled systems. When ethylcellulose (EC) is used as a membrane, the swelling agent provides an unique initiation of drug release by destruction of the EC membrane, and the time until destruction occurs is seen as a lag time in the drug release profile. The mechanism of membrane destruction consists of the following processes. First, water is taken up by TES through the outer membrane and hydrates the swelling agent causing stress against the membrane. As soon as stress exceeds membrane strength, membrane destruction is initiated. The lag time is suggested to be controlled by membrane thickness.²¹

In addition, TES has pH-independent drug release properties because the membrane destruction is not affected by environmental pH.²¹ This pH-independent destruction behavior is probably explained by: (i) pH-independent water absorption in TES, (ii) homogeneous swelling behavior of the swelling agent (low-substituted hydroxypropylcellulose, L-HPC) regardless of pH, and (iii) pH-independent membrane strength. Corresponding to the previous results of the pH-independent sedimentation volume of L-HPC powder,²¹ L-HPC layered in TES is considered to show the pH-independent swelling performance. Furthermore, when thickness of the L-HPC layer exceeds 180 μm, TES ranging from 1 to 2 mm in diameter can provide a drug-release profile with a predictable lag time, independent of the solubility of the drug incorporated.¹¹

In the present study, for the purpose of elucidating the factor most determinative of lag time, the water absorption behavior in TES with 180 μm of L-HPC layer was investigated by monitoring the weight increase of TES particles in the test fluids. The influence of a filler (talc) in the membrane on lag time was also studied.

Experimental

Materials Polystyrene spheres with a diameter of 3.2 mm (coefficient of variation (CV) for diameter = 0.05%), Polysciences INC, Warrington, PA) were used as core particles. Low-substituted hydroxypropylcellulose (L-HPC®, JP grade LH31, Shin-etsu Chemical Co., Ltd., Japan) was used as a swelling agent after sieving through a 200 mesh screen (open size: 80 μm). Ethylcellulose (EC, Ethocell® 10CP, Dow Chemical Co., Ltd., MI) was used as a water insoluble polymer membrane. Hydroxypropylmethylcellulose (HPMC, TC-5R®, Shin-etsu Chemical Co., Ltd.) was used as a binder for powder-coating of L-HPC. All the other ingredients and excipients used corresponded to Japan Pharmacopeial requirements or were of analytical grade.

Production Method of TES Sieved powder of L-HPC (450g) was powder-coated onto polystyrene balls (300g) by spraying a 5% (w/v) HPMC solution in ethyl alcohol: dichloromethane=8:2 (v/v), using a centrifugal granulator (type CF-360, Freund Industrial Co., Ltd., Japan) as described previously.²¹ Two kinds of polymer solutions for spray-coating of the membrane were prepared at an ambient temperature: 10 g of ethylcellulose (EC) or 20 g of a mixture of EC and talc [mixing ratio=1:1 (w/w)] were added to 300 ml of ethyl alcohol: dichloromethane=3:2 (w/w). Each organic solution was sprayed over the polystyrene balls covered with L-HPC powder using a fluid bed granulator (Flow-coator Min®, Freund Industrial Co., Ltd.) as described previously.

Water Absorption Study of TES One particle of TES with EC membrane was placed in JP XII 1st fluid or 2nd fluid at 37±0.5°C. At predetermined times, the TES particles were taken out and the water adhering to the particle surface was removed. Then each particle was weighed to obtain the amount of water-uptake (Qw, mg/cm²), where

\[ Q_w = \text{(increase of weight)/(initial surface area of TES)} \]

(1)

Initial surface area was calculated from the diameter of pre-tested TES. As soon as having been completed, the particle was immersed in the same solution again. When the membrane was destroyed within 30 min after re-immersion, the measured amount of water-uptake was
defined as the amount necessary for destruction. The number of samples used at each point was ten.

After destruction of the TES particles, the membrane was washed and allowed to stand for 3d at room temperature to dry. The thickness of at least three points on the dried membrane was then measured with a micrometer. The CV values for membrane thickness were less than 5%.

**Results**

**Water Absorption Study** Figure 1 shows the water absorption profiles of TES with different membrane thicknesses. These profiles were not affected by pH of the test medium. There existed a linear relation between the square of water-uptake of TES and time in accordance with Washburn's equation,\(^3\) which shows the volume of liquid penetrated into the porous body is proportional to the square root of time.

In this system, the following equation can be expressed because the square of water-uptake relates to time:

\[
Q_w^2 = K_p \cdot T
\]

where \(Q_w\) (mg/cm\(^2\)) is water-uptake of TES; \(K_p\) [(mg/cm\(^2\))^2/h] is constant; and \(T\) (h) is time.

The slopes of the absorption lines, i.e., \(K_p\), are plotted as a function of the reciprocal of EC membrane thickness (Fig. 2). A linear relationship was obtained between the two parameters \([K_p = 1.522 \times 10^3/L - 17.360, r = 0.994, L/\mu m\]).

**Relation between Lag Time and Membrane Thickness**

In Fig. 3, the water-uptake of TES necessary for destruction of the EC membrane \(Q_{bo}\) (mg/cm\(^2\)) is plotted against the membrane thickness. A pH-independent linear relation was recognized \((Q_{bo} = 0.998L - 17.554, r = 0.991)\).

By the time the membrane destruction occurs, i.e., lag time, the system has absorbed the water required for the destruction. So Eq. 2 can be described by the following expression:

\[
Q_w = K_p \cdot T_l
\]

where \(T_l\) (h) is lag time. Thus,

\[
T_l = (Q_w/K_p) \cdot (1/L + Q_{bo}/k_2)
\]

where \(k_1\) [(mg/cm\(^2\))/µm] is the water-uptake constant for destruction; \(k_2\) [(mg/cm\(^2\))^2/µm/h] is constant as represented by the slope in Fig. 2; \(Q_{bo}\) (mg/cm\(^2\)) is water-uptake of TES necessary for destruction at \(L = 0\); and \(K_p\) [(mg/cm\(^2\))^2/h] is \(K_p\) at 1/L → 0. If the relations in Figs. 2 and 3 are introduced, \(T_l\) can be defined by the following equation:

\[
T_l = (0.998L - 17.554)^2/(1.522 \times 10^3L - 17.360)
\]

As shown in Fig. 4, the observed lag time agreed with the curve calculated from Eq. 5. Therefore, it is confirmed that lag time is the function of the thickness of the membrane.

**Effect of Filler (Talc) in the Membrane on Lag Time**

The binary system of EC and talc in an equal weight ratio was used as an outer membrane to investigate the effect of a filler on lag time. In a similar way to TES coated with EC (without using talc), the water absorption kinetics accorded with Washburn's equation, that is, the square of water-uptake exhibited a linear relation with time (Fig. 5).

As seen in Fig. 6, a straight regression line was obtained
Fig. 4. Relationship between EC Membrane Thickness and Lag Time
Temperature: 37°C; test fluid: ▽, JP 1st fluid; ▲, JP 2nd fluid. The dotted curve is calculated by Eq. 4.

Fig. 5. Water Absorption Profiles of TES with EC/Talc Membrane
Temperature: 37°C; test fluid: JP 2nd fluid; thickness of EC/talc membrane: (●) 55 μm; (■) 94 μm; (▲) 133 μm; (○) 168 μm. Each point represents the mean of ten tests.

Fig. 6. Relationship Between $K_p$ and the Reciprocal of EC/Talc Membrane Thickness
Temperature: 37°C; test fluid: JP 2nd fluid; regression line: $Y = 7.642 \times 10^3 X + 1.338$, $r = 0.992$, $Y = K_p$ [mg/cm²/h], $X =$ reciprocal of membrane thickness (μm⁻¹). The dotted line shows the regression line for TES coated with EC (without talc) in Fig. 2.

by plotting the water permeation constant against the reciprocal of membrane thickness ($K_p = 7.642 \times 10^3 / L + 1.338$, $r = 0.992$). Additionally, water-uptake necessary for destruction was directly proportional to the membrane thickness (Fig. 7, $Q_D = 0.674 \times 10^{-1} L + 0.026$, $r = 0.997$). These relations crossed near the origin (Figs. 6 and 7). Therefore, Eq. 4 is reduced to

$$T_L = (k_1 / L) / (k_2 / L) = (k_1 / k_2) \cdot L^3$$  \hspace{1cm} (6)

In Fig. 8, lag time is plotted against the cube of thickness, and good linear correlation is found between the two parameters ($T_L = 0.606 \times 10^{-5} L^3 + 0.187$, $r = 0.998$).

Discussion
TES has time-controlled drug release properties with a lag time. Among the components of the system, the swelling agent has the key role in drug release, because the swelling force of the hydrated swelling agent destroys the outer membrane to create a lag time before release of the drug. The aim of this study was to clarify the relationship between the lag time and membrane thickness.

First, the water absorption kinetics in TES coated only with EC was investigated, and it was found that the square of the amount of water-uptake directly increases with time
according to Washburn’s equation (Fig. 1). Since the water permeation behavior of hydrophilic polymers is known to obey Washburn’s equation,\(^{4,5}\) the water absorption kinetics in TES is thought to be reflected by the water permeation process in the L-HPC layer. On the other hand, the water permeation was shown to depend on thickness of the EC membrane because there was a good correlation between \(K_s\) and the reciprocal of the membrane thickness (Fig. 2). Thus the water absorption in TES is suggested to be regulated not only by the L-HPC layer but also by membrane thickness.

Next, as an index of membrane strength, the water-uptake necessary for destruction was measured and was found to increase in proportion to the thickness of the membrane (Fig. 3). This relation indicates that membrane less than 17.5 \(\mu\)m is too weak to maintain the shape of TES.

Log time was found to be a function of the membrane thickness as expressed by Eq. 5. As shown in Fig. 4, this equation was confirmed by a good agreement of the observed lag times with the curve calculated from Eq. 5. This confirmed that the factor determining lag time of TES is the thickness of the membrane.

The water permeation and water-uptake for destruction did not rely on pH (Figs. 2 and 3). Thus, the pH-independent drug release is explained by the pH-independent properties of water absorption, membrane strength and swelling behavior of L-HPC.

Nielsen\(^6\) proposed that the tensile strength of polymer membrane is theoretically reduced with the volume fraction of filler. Using TES coated with EC/talc as a membrane, the effect of a filler in membrane on lag time was investigated. In accordance with the results for TES without talc, the water absorption profile fitted with Washburn’s equation (Fig. 5) and the water permeation could be controlled by the membrane thickness (Fig. 6). Compared with the membrane consisting of EC alone, the EC/talc membrane showed a smaller value of \(K_s\) (Fig. 6). The reason for this decrease is postulated to be as follows: (i) creation of a denser membrane by the addition of talc, or (ii) change of membrane structure with increased thickness.

It has been reported that the strength of HPMC film is decreased by the addition of talc.\(^8,9\) In the plot of the water-uptake for destruction against membrane thickness, the slope for the EC/talc membrane was only one-fifteenth of that for the EC membrane (Fig. 7). The decrease might be caused by the loss of membrane strength due to the talc addition.

As described by Eq. 6, lag time of TES coated with EC/talc membrane is believed to be controlled by the cube of the membrane thickness (Fig. 8). Indeed, concerning the \(k_1/k_2\) value in Eq. 6, the observed value \([0.606 \times 10^{-5}\) (h/\(\mu\)m\(^3\)]) was almost the same as the value \([0.594 \times 10^{-5}\) (h/\(\mu\)m\(^3\)]) calculated by \(k_1\) and \(k_2\) obtained in Figs. 6 and 7.

In conclusion, the determinant of lag time of TES was confirmed to be the thickness of the membrane. Moreover, the addition of talc in EC membrane shortened lag time because it reduced membrane strength.

References