Controlled Release of Drugs from Hydrogel Matrices

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Synopsis

A series of polymers with wide ranges of water absorptivity were prepared and utilized as matrices for the controlled release of drugs. The drugs were introduced into the matrices by use of an appropriate organic solvent. Release rates of erythromycin and erythromycin estolate from hydrogel were analyzed kinetically and found to conform to Higuchi's equation, that is, $M_t = A(2DtC_sC_0)^{1/2}$, where M_t is the accumulated amount of released drug at time t, A is the surface area, D is the diffusion coefficient, C_s is the solubility of drug in the hydrogel matrix, and C_0 is the initial drug content of the preparation in the swollen state. The relationship between the water content of hydrogel and the diffusion coefficient of erythromycin in hydrogel is expressed by the equation $D = 3.03 \times 10^{-10} W^{3.03}$ (cm^2/sec), where W is the water content (%). The release rate of drug can be controlled quantitatively by adjustment of the water content of the hydrogel matrix. A guide to the design for the preparation is suggested.

INTRODUCTION

Controlled release is an important step toward improving the delivery of a biologically active agent to its target. To release a drug intracavitarily for a certain period at a rate as constant as possible, it is desirable to insert the proper preparation of the drug into the cavity. Hydrogel is an acceptable material to insert from the standpoint of biocompatibility because it generally has a low stimulation to living tissue. Conventionally, the hydrogel is dipped in aqueous drug solution before insertion.[1,2] In such a method, however, there is a tendency for drugs that are easily incorporated into hydrogel to be released rapidly, and thus the desired effect is not maintained long enough.

In this report we describe a method of preparing drug–hydrogel combinations that possess desirable properties of drug release rates accompanied by good acceptability by the test animals. The method consists of (a) introduction of drug into the gel using an organic solvent in which the drug has high solubility and a matrix polymer with a large swelling ratio, (b) control of the drug release rate by adjustment of the swelling ratio of matrix polymer in water. Ocular inserts made by application of this principle were evaluated from the viewpoint of trachoma therapy by R. L. Nichols and his associates at the Harvard School of Public Health, the results of which will be reported elsewhere.

EXPERIMENTAL

Preparation of Matrix Polymers

A mixture of methyl methacrylate, ethyl acrylate, and N-vinylpyrrolidone together with initiator and crosslinking agents was polymerized in the space between two glass plates pretreated with silicone. Polymer was obtained in the

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form of a thin sheet, the thickness of which was adjusted to 0.2–0.3 mm in the swollen state in water unless otherwise stated. The degree of swelling of the polymers in water or organic solvents was regulated by the polymer composition and degree of crosslinking. The matrix polymer was extracted thoroughly with ethanol before a drug was introduced into it.

The swelling ratio of the polymer, Q, and the water content of the hydrogel, W, are defined as

$$Q = \frac{\text{weight of swollen gel (at 23°C)}}{\text{weight of dried gel}}$$

$$W(\%) = 100\,\frac{\text{weight of hydrogel} - \text{weight of dried gel}}{\text{weight of hydrogel (at 30°C)}}$$

Preparation Process of Drug Hydrogel Combinations

A sheet of matrix polymer was impregnated with organic solvent solution containing an antibiotic. The solvent absorbed in the gel was removed by evaporation under reduced pressure or lyophilization. Ethanol, dioxane, or benzene was used as solvent.

Erythromycin and its estolate were isolated from the commercial preparations by extraction with ethyl acetate (Shionogi Pharmaceutical Co., Ltd.) Elemental analysis of these extracted drugs (C, H, N, and S) agreed well with the calculated data.

Measurement of Release Rate

A sheet of gel containing antibiotic was placed in physiological saline at room temperature for 2 hr to be swollen. From the swollen gel sheet, round test pieces were stamped out, the total surface of each piece being 1.58 cm^2. The side area of a test piece was neglected when the piece was thinner than 0.4 mm. But when a test piece was thicker than 2 mm, the side was belted with silicone rubber to prevent the elution of drug from there. That was the case for elution of erythromycin from a hydrogel of more than 30% water content.

A preswollen test piece of drug–hydrogel combination was put in 5 ml physiological saline containing 0.9% sodium chloride and 0.08% sodium bicarbonate at 30°C, with no agitation unless stated. The elution medium was replaced every 24 hr and the drug concentration in the medium was determined. At the end of the elution procedure, the antibiotic remaining in the hydrogel was extracted with ethanol and determined. The amount of the antibiotic was measured either chemically by the sulfuric acid method[3] or biologically by the cup method using *Bacillus subtilis* PCI 219 as the standard strain. Both methods gave similar results. Erythromycin had an activity 1.4 times that of an equal weight of erythromycin estolate. Since the molecular weight of the latter is 1.44 times that of the former, this fact indicates these two antibiotics have the same molar activity.

RESULTS AND DISCUSSION

Preparation of Drug–Hydrogel Combination

The most important property of the polymer matrices for controlled-release preparations is the degree of swelling in water and in some organic solvents. It is a function of the polymer composition and the degree of crosslinking. Table I shows the swelling ratios of the polymers in water and in the organic solvents tested. The data show that the swelling ratio in water can be altered widely while that in an organic solvent is kept almost constant for some polymer systems. In most cases, the swelling ratio in organic solvent is higher than that in water. This property is favorable for the introduction of antibiotics into matrix gel.

In the present report, we studied the release profile of erythromycin and erythromycin estolate. The former has a relatively higher solubility in the aqueous elution medium described before, that is, 2.7 mg/ml at 30°C, while the latter has a lower solubility, 0.35 mg/ml. As both antibiotics are readily soluble in ordinary organic solvents, gel can be easily impregnated with either antibiotic by being placed in the drug solution overnight. As shown in Table II, the measured drug concentrations in the gel agree approximately with the values calculated by eq. (1),

$$C_d = \frac{1000C(Q-1)/d}{[C(Q-1)/d] + 1000} \tag{1}$$

TABLE I
Compositions and Swelling Ratios of Matrix Polymers

Composition,[a] wt-%					Swelling ratio Q			
NVP	MMA	EA	VAc	GMA	Water	Benzene	Ethanol	Dioxane
85	5	10	—	—	9.1	—	—	8.1
82	5	13	—	—	6.5	—	9.1	—
78	12	10	—	—	5.1	—	8.3	—
40	—	—	55	5	4.6	—	—	12.5
60	15	25	—	—	3.0	4.1	—	—
54	16	30	—	—	2.4	—	7.6	12.5
48	15	37	—	—	2.1	5.9	—	—
45	10	40	—	5	1.8	—	—	—
40	10	50	—	—	1.5	—	6.5	—
30	10	55	—	5	1.3	—	—	8.3
20	10	70	—	—	1.1	7.6	—	—

[a] NVP = N-vinylpyrrolidone; MMA = methyl methacrylate; EA = ethyl acrylate; VAc = vinyl acetate; GMA = glycidyl methacrylate.

TABLE II
Gels Impregnated with Erythromycin[a]

Solvent	Q	C, mg/cm^3	C_d, mg/g	
			Calcd	Obsd
Ethanol	7.1	250	660	622
Benzene	7.6	100	428	401
Benzene	7.6	50	272	294
Benzene	7.6	10	70	93

[a] Swelling ratio of the polymer in water is 1.25.

where C_d is the drug content of the dried gel (mg/g), C is the concentration of the drug in solution (mg/cm^3), and d is the density of the solvent. This equation is based on the assumption that both the solubility of the drug in the organic solvent, C, and the swelling ratio of the polymer, Q, are kept the same in the drug–solvent–polymer ternary system as in each binary system. Furthermore, it is assumed that the density of the mixture of the drug and the polymer are equal to that of water.

Substitution of C and Q defined as

$$C = 1000d(\text{drug})/\text{solvent} \qquad (\text{mg/cm}^3)$$

$$Q = (\text{polymer} + \text{solvent})/\text{polymer}$$

into eq. (1) results in the approximate definition of C_d where "drug," "polymer," and "solvent" stand for respective weights.

$$C_d \fallingdotseq 1000(\text{drug})/(\text{polymer} + \text{drug}) \qquad (\text{mg/cm}^3)$$

A portion of the drug is leached out in the swelling procedure (30°C, 2 hr in physiological saline) before release. The loss is larger the higher the swelling ratio in physiological saline.

Release Rate and State of Drug

Erythromycin estolate is undoubtedly dispersed as fine particles in the polymer matrix, because the transparency of the hydrogel is lost by introduction of the antibiotic and then recovered as drug is released. In Figure 1, the region filled with drug particles is observed distinctly, surrounded by a transparent layer from which the drug particles have been depleted. On the other hand, the state of erythromycin is not apparent because the gel containing the drug is transparent in both the dry and wet states. Higuchi[4] derived eqs. (2) and (3) for elution of drug dispersed in polymer slab, using the model illustrated in Figure 2:

$$\frac{M_t}{A} = (2DtC_sC_0)^{1/2} \qquad \text{for } C_0 \gg C_s \tag{2}$$

$$\frac{d(M_t/A)}{dt} = 1/2(2DC_sC_0/t)^{1/2} \tag{3}$$

where M_t = the amount of drug released during time t, A = surface area of preparation, D = diffusion coefficient (cm^2/sec), C_s = solubility of drug in hydrogel (mg/cm^3), and C_0 = initial drug concentration in hydrogel (mg/cm^3).

Baker and Lonsdale proposed eq. (4) for the case in which drug is dissolved in the polymer[5]:

$$\frac{M_t}{A} = 2C_0(Dt/\pi)^{1/2} \qquad \text{for } 0 < M_t/M_\infty < 0.6 \tag{4}$$

The data in the case of erythromycin are plotted in Figures 3 and 4. The slopes of the straight lines in Figure 3, 0.52 at two days and 0.66 at five days, better approximate Higuchi's equation. Furthermore, the validity of the dispersed drug model is supported by the fact that reasonable D values are obtained when calculated from eq. (2) in the case of erythromycin, as shown in Table III, though the unaccountably small values below 10^{-10} cm^2/sec result from eq. (4) (data not

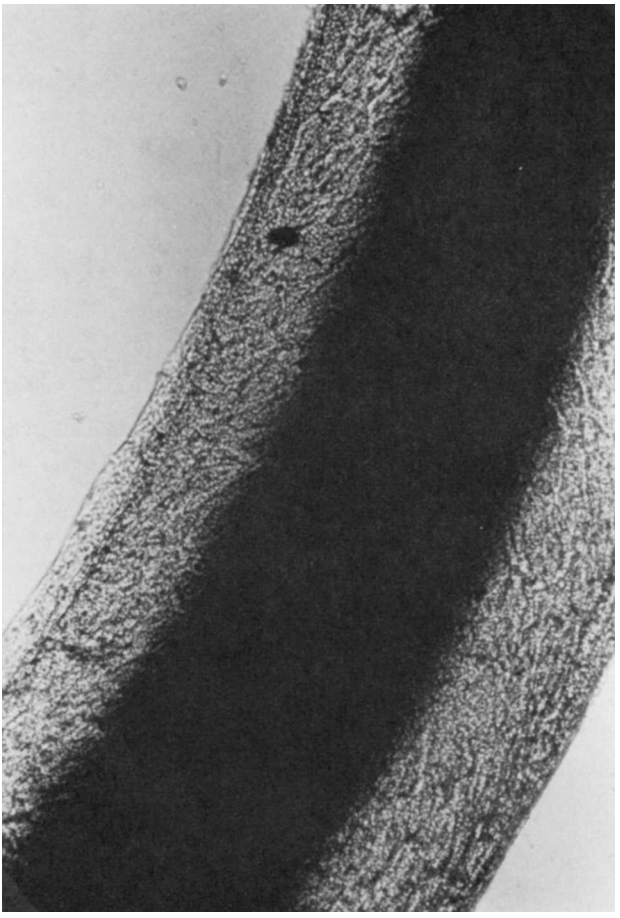

Fig. 1. Cross-sectional micrograph of a gel sheet in the course of releasing erythromycin estolate. Thickness is ca. 0.3 mm.

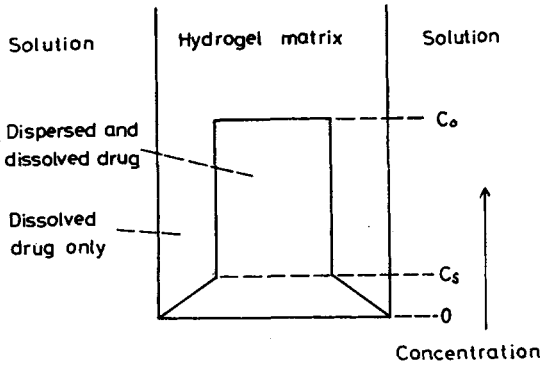

Fig. 2. Hypothetical diagram for drug distribution in a polymer slab in contact with a perfect sink.

shown). To calculate the diffusion coefficient D from the data of Figure 4 and eq. (2), we assumed eq. (5), since we have not measured C_s directly. This means

$$C_s = C_w[1 - (C_0/1000)](W/100) \quad (5)$$

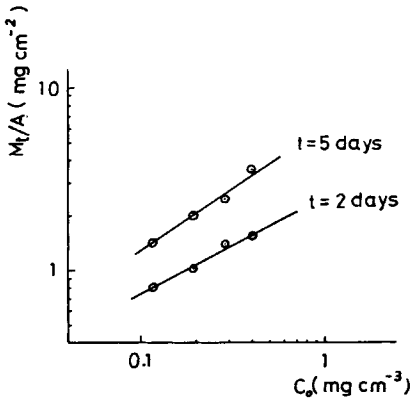

Fig. 3. Relationship between amount of released erythromycin and initial drug content.

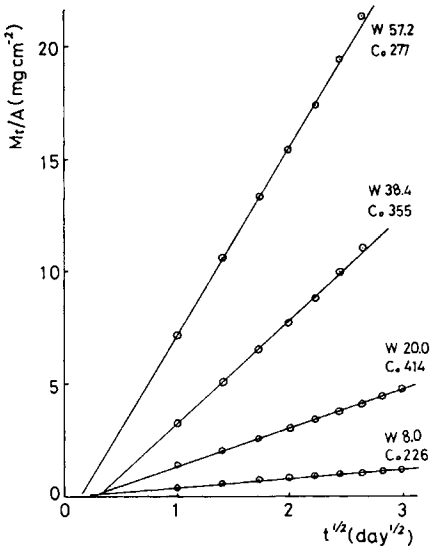

Fig. 4. Release of erythromycin from hydrogel. W in %, C_0 in mg/cm^3.

that the solubility of the drug in the aqueous elution medium and the water content of the hydrogel, are both kept the same in the drug–aqueous medium–polymer ternary system as in each binary system, under the approximation that both the densities of the drug and the polymer are equal to that of water. The definition of C_s results from the substituion of the following formulas into eq. (5):

$$C_w = 1000 \text{ (dissolved drug)/water} \qquad (\text{mg/cm}^3)$$

$$C_0/1000 = \text{total drug/(total drug + polymer + water)} \qquad (\text{mg/cm}^3)$$

$$W/100 = \text{water/(water + polymer)}$$

The release of erythromycin estolate is remarkably affected by agitation, as can be seen in Figure 5, while that of the erythromycin is not influenced at all. The amount of released erythromycin estolate is proportional to the square root

TABLE III
Estimates of Diffusion Coefficients

W, %	DC_s, cm² mg/sec cm³		D, cm²/sec	
	Eryth.	Eryth. est.	Eryth.	Eryth. est.
100			3.2×10^{-6} [a]	2.5×10^{-6} [a]
73		1.6×10^{-7}		1.4×10^{-6}
57	1.3×10^{-6}		1.2×10^{-6}	
38	3.3×10^{-7}		4.9×10^{-7}	
33		5.2×10^{-8}		9.9×10^{-7}
23				
20	3.8×10^{-8}		1.2×10^{-7}	
14		4.5×10^{-8}		7.3×10^{-7}
8	3.5×10^{-9}		2.4×10^{-8}	
5		7.1×10^{-9}		7.5×10^{-7}
Natural rubber			8.4×10^{-10} [a]	3.5×10^{-10} [a]

[a] Estimates from molecular weights.[5]

of time under agitation. In this case also, equation (2) fits well without agitation if water content of hydrogel is as low as 5%. These observations indicate the boundary layer effects, which will be discussed later.

Relationship Between Release Rate and Water Content

Table III shows DC_s and D calculated by fitting eqs. (2) and (5) to the data shown in Figures 4 and 5. In the case of erythromycin estolate, the calculated D values are so large that they are of comparable order to the estimate for the antibiotic in pure water. As this is patently impossible, the solubility of erythromycin estolate must be larger than the calculated values from eq. (5), especially in the lower water content region because of its affinity to the matrix polymer.

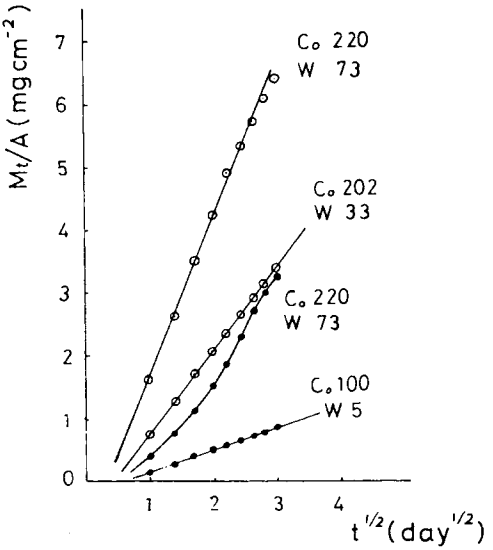

Fig. 5. Release of erythromycin estolate from hydrogel. (○) with shaking; (●) without shaking. W in %, C_0 in mg/cm³.

In the case of erythromycin, the calculated D values seem to be reasonable, because they are between the estimates in water and that in natural rubber. In this case, a plot of log D versus log W gives a straight line as shown in Figure 6, which is expressed by eq. (6), where units of D and W are cm^2/sec and %, respectively:

$$D = 3.03 \times 10^{-10} W^{2.03} \tag{6}$$

Consequently, the release rate of the antibiotic at a given time is able to be calculated from eq. (7) which is obtained by substitution of eqs. (5) and (6) into (3):

$$\frac{dM_t/dt}{A} = 1.23 \times 10^{-6} C_w{}^{1/2} t^{-1/2} W^{1.52} C_0{}^{1/2} [1 - (C_0/1000)]^{1/2} \quad \text{(mg/cm}^2\text{·sec)} \tag{7}$$

Assuming C_0 = 300 mg/cm^3 and t = one day = 8.64×10^4 sec, we obtain eq. (8):

$$\frac{dM_t/dt}{A} = 6.06 \times 10^{-8} C_w{}^{1/2} W^{1.52} \quad \text{(mg/cm}^2\text{ sec)}$$

$$= 5.24 \times 10^{-3} C_w{}^{1/2} W^{1.52} \quad \text{(mg/cm}^2\text{ day)} \tag{8}$$

The curved lines including dashed ones in Figure 7 show the relationship between $(dM_t/dt)/A$ and W calculated from eq. (8) in the case C_w = 2.7 or 0.35 mg/cm^3. Naturally, the observed values are in fair agreement with the calculated ones in the case of erythromycin.

Boundary Layer Effects

Equation (7) or (8) holds for cases in which the diffusion of drug within the gel is rate determining, whereas the situation is different when erythromycin estolate is released from gel of high water content without agitation. The latter

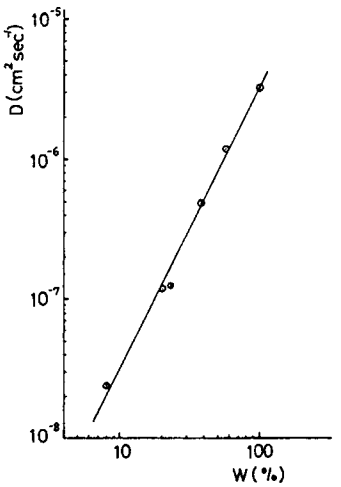

Fig. 6. Relationship between diffusion coefficient of erythromycin and water content of hydrogel.

case can be dealt with in a similar way to the treatment of the boundary layer effects by Baker and Lonsdale.[5]

Equation (9) expresses the diffusion rate of the solute in the elution medium phase, L being the thickness of the boundary layer model:

$$J = DC_{x=0}/L \tag{9}$$

where $J = (dM_t/dt)/A$, x = distance from gel surface, and $C_{x=0}$ = drug concentration in the elution medium at $x = 0$.

Assuming the flux to be J_{max} when agitation is sufficient,

$$J = J_{max}[1 - (C_{x=0}/C_w)] \tag{10}$$

From Figure 5 at t = one day, in the case of erythromycin estolate,

$$J_{max} = 1.25 \text{ mg/cm}^2 \text{ day}$$

$$J = 0.39 \text{ mg/cm}^2 \text{ day}$$

$$C_{x=0}/C_w = 0.688$$

By substituting the above values in eq. (9), we obtain $L = 0.13$ cm. The upper limit of J is given below, being termed J',

$$J' = DC_w/L \tag{9'}$$

because the upper limit of $C_{x=0}$ is C_w. In Figure 7, experimental data are found near the value of J', which is shown as a plateau at 0.58 mg/cm^2 day.

In the case of erythromycin, J' is evaluated as 5.7 mg/cm^2 day in the same way, by L being assumed equal to the above value, although it depends ordinarily on the value of C_w. It is anticipated from Figure 7 that the diffusion in the boundary layer outside the gel becomes a rate-determining step above 70% water content even in the case of erythromycin.

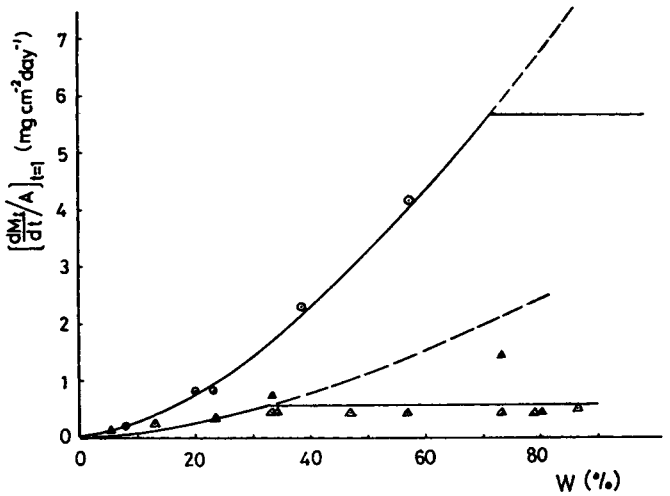

Fig. 7. Release rate as function of water content of hydrogel: (○) erythromycin, without shaking; (△) erythromycin estolate, without shaking; (▲) erythromycin estolate, with shaking.

Design of Preparation

From Figure 7, the release rate of drug is seen to be kept nearly constant by the function of boundary layer effects. The boundary layer effects in vivo, however, are hard to quantify because the hydrodynamic conditions are usually unknown. Therefore, it is desirable to avoid boundary layer effects and control the release of drug by its diffusion rate within the hydrogel. In that case, the release rate can be calculated from eq. (7).

In this case, however, the initial release rate is so high that prewashing is recommended. The technique consists in releasing the drug from the gel for a certain period of time before use. If the symbols t_w and t_r express the prewashing time and scheduled period of application, respectively, the substitutions of t_w and $t_w + t_r$ into t in eq. (7) lead to eqs. (11) and (12), which express the conditions of substantially the initial and final stages in the application of the preparation:

$$\left(\frac{dM_t}{dt}\right)_{t_w} = 1.23 \times 10^{-6} A C_w^{1/2} t_w^{-1/2} W^{1.52} C_0^{1/2} [1 - (C_0/1000)]^{1/2} \quad (11)$$

$$\left(\frac{dM_t}{dt}\right)_{t_w+t_r} = 1.23 \times 10^{-6} A C_w^{1/2} (t_w + t_r)^{-1/2} W^{1.52} C_0^{1/2} [1 - (C_0/1000)]^{1/2} \quad (12)$$

The values of t_r, $(dM_t/dt)_{tw}$, and $(dM_t/dt)_{t_w+t_r}$ should be given on a medical basis. It is convenient from the standpoint of preparation that the difference between the release rates at the initial and final stages is specified as large as possible. The ratio of initial to final release rate is expressed by eq. (13):

$$\left(\frac{dM_t}{dt}\right)_{t_w} \Big/ \left(\frac{dM_t}{dt}\right)_{t_w+t_r} = \frac{(t_w + t_r)^{1/2}}{t_w^{1/2}} = [1 + (t_r/t_w)]^{1/2} \quad (13)$$

As $(dM_t/dt)_{t_w}$, $(dM_t/dt)_{t_w+t_r}$, and t_r are given as mentioned before, t_w is calculated by eq. (13). Then A, W, and C_0 can be set so as to satisfy eq. (11) or (12), as C_w is a constant inherent in the drug. As these parameters are not fixed at single values mathematically, they can be adjusted to make the size, hardness, and biocompatibility of the preparation most suitable under the conditions expressed by eq. (11) or (12).

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