Kinetics of Swelling of Compressed Cellulose Matrices: A Mathematical Model

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Purpose. A model for swelling time course of compressed cellulose matrix is presented.
Methods. The model incorporates the two most important features: water penetration by diffusion and volume change due to swelling. Approximations of the model for small t values and for large t values are also derived, which are utilized in a handy routine for estimation of swelling parameters.
Results. The observed time courses of thickness change with compressed matrices of methyl cellulose and hydroxypropyl cellulose agree well with the calculated values of the proposed model.
Conclusions. The proposed model is compatible with the observed swelling kinetics.

KEY WORDS: swelling; compressed matrix; diffusion; methyl cellulose; hydroxypropyl cellulose.

INTRODUCTION

In pharmacy, swelling kinetics is important in the disintegration of tablets and capsules and in how it affects the drug release from sustained-release dosage forms based on compressed cellulose matrices. When a compressed cellulose matrix is placed in contact with water, the penetrant enters the matrix, forming a swollen phase in the wetted region. Subsequently the drug is released.

Robinson (1) found empirically that a second-order rate equation described the rate of swelling in terms of the one-dimensional increase in thickness of a gelatin film coated onto a solid support.

$$t/\Delta T = a + bt \quad (1)$$

That is, a plot of time t divided by the increase in thickness ΔT against time was a straight line of intercept a and slope b. Rearranging Eq. 1, we obtain:

$$\Delta H = \frac{t}{a + bt} \quad (2)$$

where ΔH is the increase in thickness of the matrix.

Schott (2) derived Eq. 3 assuming that diffusion controlled swelling follows first-order kinetics:

$$\log \frac{W_\infty}{W_\infty - W} = kt \quad (3)$$

where W_∞ is the maximum uptake of the swelling medium. Converting weight increase into a one-dimensional increase in thickness and then rearranging, we obtain:

$$\Delta H = (H_\infty - H_0) * (1 - \exp(-kt)) \quad (4)$$

where H_∞ and Ho are the fully swollen thickness and the initial dry thickness of the matrix, respectively.

Korsmeyer *et al.* (3) developed a mathematical model incorporating the two most important features of swelling: water penetration by diffusion and volume changes due to swelling.

The aims of this report are: (a) experimental verification of the adequacy of the treatment for the kinetics of swelling proposed by Korsmeyer *et al.* (3); (b) derivation of approximations of the model for two extremes of time values; and (c) an application of the expressions for a handy routine for estimation of swelling parameters, using observed data of swelling of hydrophilic cellulose matrices.

THEORETICAL

Description of the Model

Water enters the matrix following Fick's law of diffusion:

$$\frac{\partial C}{\partial t} = \frac{D}{\tau_0} \frac{\partial^2 C}{\partial x_0^2} \quad (5)$$

where C is water concentration in the matrix relative to the equilibrium concentration, D is the diffusion constant of water in a fully swollen matrix and τ_0 is the tortuosity of the dry matrix.

The boundary conditions are:

$$t = 0, \quad C = 0, \quad \text{at} \quad 0 \le x_0 < H_0$$
$$t > 0, \quad C = 1, \quad \text{at} \quad x_0 = H_0$$
$$\frac{\partial C}{\partial x_o} = 0, \quad \text{at} \quad x_0 = 0$$

Equation 5 has a simple analytical solution:

$$C = 1 - \frac{4}{\pi} \sum_{n=0}^{\infty} \frac{(-1)^n}{2n + 1} \cos \frac{(2n + 1)\pi x_0}{2H_0} \times \exp\left(-\frac{(2n + 1)^2\pi^2 Dt}{4H_0^2\tau_0}\right) \quad (6)$$

As shown in Fig. 1, the polymer swells depending on the water content C and increases the thickness of the polymer matrix embedded in a tubular support. This is given by Eq. 8:

$$dx = \frac{dx_0}{1 - \nu C} \quad (7)$$

$$\Delta H = H - H_0 = \int_0^{H_0} dx - \int_0^{H_0} dx_0 = \int_0^{H_0} \frac{\nu C}{1 - \nu C} dx_0 \quad (8)$$

where ν is a parameter governing the thickness of maximum swelling. We assume that the increase in the matrix thickness due to swelling is compensated with the decrease of tortuosity.

$$\tau = (1 - \nu C)^2 \tau_0 \quad (9)$$

$$\tau dx^2 = \tau_0 \, dx_0^2 \quad (10)$$

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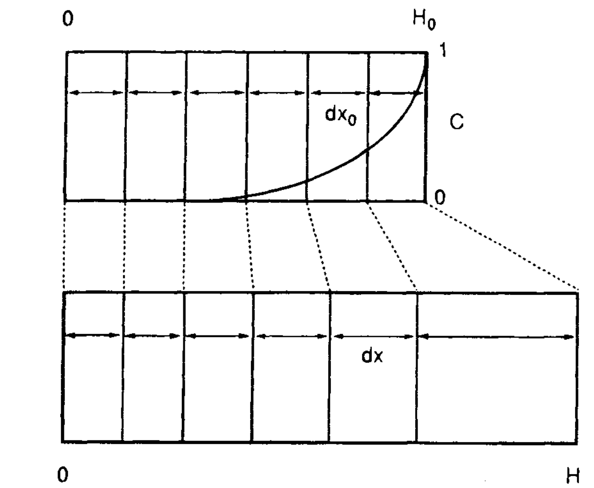

Fig. 1. Schematic representation of the proposed model of swelling.

$$dx = \frac{dx_0}{1 - \nu C}, \quad H = \int_0^{H_0} \frac{dx_0}{1 - \nu C}$$

The water path in the matrix or the effective thickness of the matrix remains constant and Eq. 6 still holds after the matrix has swollen.

Approximation of ΔH for Large t

For large values of t, C is written as:

$$C = 1 - \frac{4}{\pi} \cos \frac{\pi x_0}{2H_0} \exp\left(-\frac{\pi^2 Dt}{4H_0^2 \tau_0}\right) \tag{11}$$

Substituting Eq. 11 into Eq. 8 and integrating, we obtain an approximation of ΔH for large t:

$$\Delta H = \frac{\nu H_0}{1 - \nu}\left[1 - \frac{8}{(1 - \nu)\pi^2} \exp\left(-\frac{\pi^2 Dt}{4H_0^2 \tau_0}\right)\right] \tag{12}$$

If $8/(1 - \nu)\pi^2 = 1$ or $\nu = 1 - 8/\pi^2 = 0.18943$, Eq. 12 coincides with Eq. 4, where $\nu H_0/(1 - \nu) = H_\infty - Ho$ and $\pi^2 D/4Ho^2 \tau_0 = k$. Derivation of Eq. 12 is shown in the Appendix.

Approximation of ΔH for Small t

For small t, one-dimensional diffusion in a medium bounded by two parallel planes can be treated as the diffusion in a semi-infinite medium. From this we can write:

$$C = 1 - \mathrm{erf}\left(\frac{H_0 - x_0}{2\sqrt{Dt/\tau_0}}\right) \tag{13}$$

Using a hyperbolic tangent for approximation of the error function:

$$\mathrm{erf}(x) \cong \tanh\left(\frac{2}{\sqrt{\pi}} x\right) \tag{14}$$

$$C = 1 - \tanh\left(\frac{H_0 - x_0}{\sqrt{\pi Dt/\tau_0}}\right) \tag{15}$$

After substituting Eq. 15 into Eq. 8, integrating and simplifying, we obtain an approximation of ΔH for small t:

$$\Delta H = \frac{\nu \log(2 - 2\nu)}{1 - 2\nu} \sqrt{\pi Dt/\tau_0} \tag{16}$$

Derivation of Eq. 16 is shown in the Appendix.

MATERIALS AND METHODS

Materials

Indomethacin (IM) powder was purchased from Nacalai Tesque, Inc., Japan. Methyl cellulose (50 cP, MC50) and hydroxypropyl cellulose (140 cP, HPC140) were purchased from Wako Pure Chemical Industries (Tokyo, Japan). All other materials used were of analytical reagent grade.

Matrix Preparation

IM was dried at 60°C for 8 hours before passed through a 42 mesh sieve. All types and grades of polymer were also passed through a 42 mesh sieve before use. Physical mixture of IM and polymer (MC50 and HPC140) were prepared to obtain the drug:polymer ratio of 1:2. The mixture was directly compressed by a tableting machine (Erweka Type EKO, Germany) to obtain matrix with 400 mg weight, 12 mm diameter and 8 to 11 kg crushing strength.

Swelling Experiment

The swelling was performed in the swelling experiment unit shown in Fig. 2, in order to (1) observe the axial swelling, (2) control the penetration to occur only from the upper surface of the matrix, and (3) determine the swelling without disturbing or destroying the system. The bottom and edge coating of the matrix were obtained by using hard paraffin. The coat-matrix

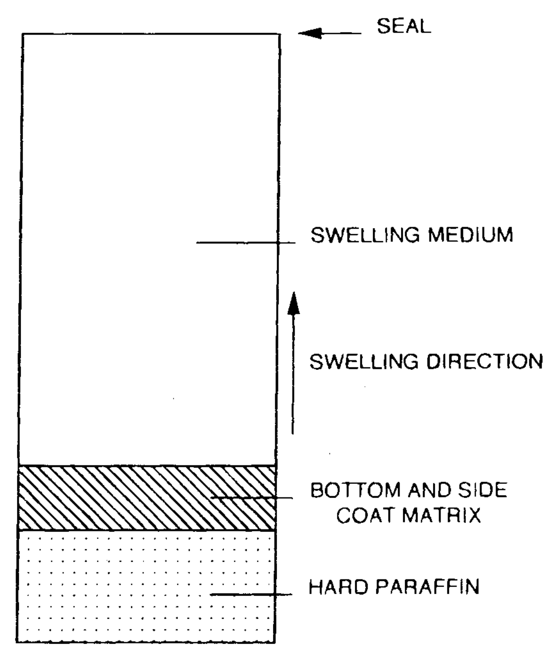

Fig. 2. Swelling experiment unit.

was then fixed onto the flat-surface base made of hard paraffin which was colored by using 0.5 % w/w Sudan III in order to state the matrix base.

The swelling was maintained at 37°C by using a thermoregulated water bath. In each unit the timing was started as soon as the medium (5 ml, 37°C) touched the surface of the matrix. In order to compare the swelling data with the drug release data, phosphate buffer (pH 6.2) which was used as a release medium in the release study (data not shown) was used as the swelling medium. The upper part of the unit was sealed to prevent the evaporation of the medium. At each time interval the swelling was measured directly through the matrix height (H) using a vernier caliper. The swelling was observed for more than 8 hours. Four replicate measurements were carried out for each polymer.

Evaluation of Eqs. 6 and 8

For given values of ν, D/τ_0 and t, the n value that satisfies the following condition was obtained:

$$\frac{(2n+1)\pi}{2H_0}\sqrt{Dt} \geq 5$$

The summation of Eq. 6 was evaluated up to that n value. Consequently, the truncation error of C is less than e^{-25} or 1.93×10^{-11}.

Integration of Eq. 8 was performed by Simpson's rule, setting the fractional accuracy to 10^{-6}, using subroutine qsimp (4).

Handy Routine for Estimation of Swelling Parameters

Rearrangement of Eqs. 12 and 16 gives Eqs. 17 and 18, respectively.

$$\nu = \frac{\Delta H_2}{B + \sqrt{B^2 - \Delta H_2(\Delta H_2 + H_0)}} \qquad (17)$$

where

$$B = \Delta H_2 + \frac{H_0}{2}\left\{1 - \frac{8}{\pi^2}\exp\left(-\frac{\pi^2 t_2 D}{4H_0^2\tau_0}\right)\right\}$$

$$D/\tau_0 = \frac{1}{\pi t_1}\left[\frac{(1-2\nu)\Delta H_1}{\nu \log(2-2\nu)}\right]^2 \qquad (18)$$

Using two sets of swelling data; observed at early stage (t_1, ΔH_1) and at later stage (t_2, ΔH_2), swelling parameters, D/τ_0 and ν, were estimated as follows:

[Step 1] Assuming very large value for D/τ_0 in Eq. 17, ν value was estimated as $\nu = \Delta H_2/(\Delta H_2 + Ho)$.

[Step 2] Substituting ν value obtained in the previous step into Eq. 18, D/τ_0 value was estimated.

[Step 3] Substituting D/τ_0 value obtained in the previous step into Eq. 17, ν value was estimated.

[Step 4] Go to [Step 2].

Converged D/τ_0 and ν values were obtained in alternating steps 2 and 3.

Calculations

Model adaptations and simulations were carried out on an IBM-compatible personal computer (Mistation 3S, MITAC-Japan, Tokyo). Programs were written in FORTRAN77. The algorithm proposed by Berman *et al.* (5), which is essentially of a damping Gauss-Newton method, was used for nonlinear model adaptations.

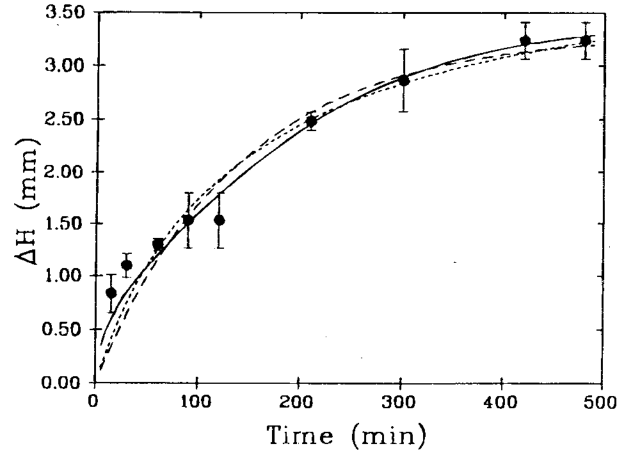

Fig. 3. Observed swelling time course of MC50-IM matrix. The solid, dotted, and broken curves represent respectively the least squares computer fitting of the proposed model (Eqs. 6 and 8), Eq. 2 and Eq. 4, to observed increase in the thickness of the MC50-IM matrix. Model parameters are as shown in Table I. Points and vertical bars: mean ± S.D. n = 4.

RESULTS AND DISCUSSION

Observed swelling of MC50-IM and HPC140-IM matrices are shown in Figs. 3 and 4, respectively. The solid curves represent the theoretical values of ΔH obtained by least-squares adaptation of the model (Eqs. 6 and 8). Dotted and broken curves in Fig. 3 represent the calculated values of ΔH obtained by least squares adaptation of Eq. 2 and Eq. 4, respectively. Agreements of observed data and calculated values are fairly good and confirm the compatibility of the proposed model with

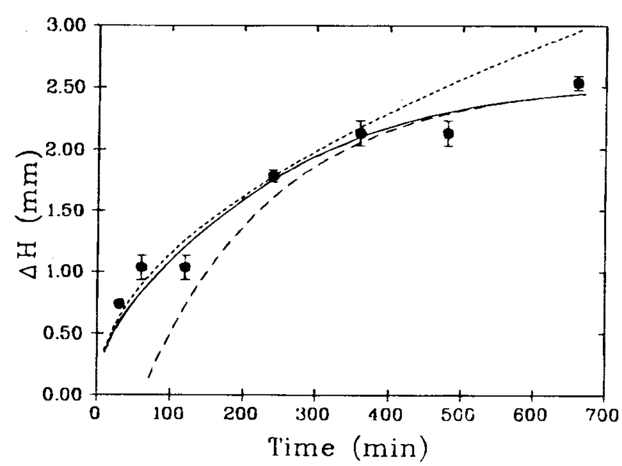

Fig. 4. Observed swelling time course of HPC140-IM matrix. The solid curve represents the least squares computer fitting of the proposed model (Eqs. 6 and 8) to the observed increase in the thickness of the HPC140-IM matrix. The dotted and broken curves show approximations for small t values and for large t values, respectively. Model parameters are as shown in Table I. Points and vertical bars: mean ± S.D. n = 4.

Table I. Model Parameters[a] and AIC values

		MC50-IM	HPC140-IM
	Ho	2.967	3.467
	(mm)	±0.058	±0.058
Eq. 2	a	33.026	49.699
	(min/mm)	±6.003	±11.005
	b	0.24236	0.34205
	(mm^{-1})	±0.02485	±0.03544
	AIC	−2.3484	−7.0983
Eq. 4	H∞	6.2492	5.8463
	(mm)	±0.2651	±0.2035
	k	0.00726	0.00639
	(min^{-1})	±0.00155	±0.00165
	AIC	−0.0209	−4.5227
Eqs. 6 & 8	D/τ_0	0.02782	0.02733
	(mm^2/min)	±0.00379	±0.00573
	ν	0.53458	0.42176
		±0.01391	±0.01903
	AIC	−10.299	−10.337

[a] Values ± S.D.

observed data. Dotted and broken curves in Fig. 4 represent approximations for small t values and for large t values, respectively.

Model parameters are shown in Table I along with AIC values. Among the equations examined, the proposed model gives the lowest AIC values indicating the superior compatibility with the observed data.

Mean values of times and changes in swelling height observed during the first 120 minutes and those obtained in the last two observations were calculated and used for the estimation of swelling parameters, as t_1, ΔH_1 and t_2, ΔH_2, respectively, in the handy routine. Converged values of D/τ_0 and ν were 0.02528 mm^2/min and 0.54025 for MC50-IM, and 0.02641 mm^2/min and 0.41809 for HPC140-IM. Compared with the values shown in Table I, differences are less than 10 % for D/τ_0 and around 1 % for ν. These results confirm the adequacy of the handy routine for estimation of swelling parameters.

Assuming that the tortuosity τ is unity in the fully swollen polymer, and rearranging Eq. 9, τ_0 is evaluated as $\tau_0 = 1/(1 - \nu)^2$. Using the parameter values of Table I. diffusion coefficients of water in the fully swollen MC50-IM and HPC140-IM are calculated as 2.1358 and 1.3620×10^{-5} cm^2/sec, respectively. The reported diffusion coefficients of $^1H^2H^{16}O$ in water are 1.294, 1.743 and 2.261×10^{-5} cm^2/sec at 5, 15 and 25°C, respectively (6). The fact that the parameter values derived from the model are reasonable, the acceptability of the proposed model is reconfirmed.

APPENDIX

Derivation of Eq. 12

Substituting Eq. 11 into Eq. 8, we obtain:

$$\Delta H = \int_0^{H_0} \frac{\nu - \frac{4\nu}{\pi}\exp\left(-\frac{\pi^2 Dt}{4H_0^2\tau_0}\right)\cos\left(\frac{\pi x_0}{2H_0}\right)}{(1-\nu) + \frac{4\nu}{\pi}\exp\left(-\frac{\pi^2 Dt}{4H_0^2\tau_0}\right)\cos\left(\frac{\pi x_0}{2H_0}\right)} dx_0 \quad (1A)$$

Changing variable $\pi xo/2Ho$ to X, we have $dxo = (2Ho/\pi)dX$ and:

$$\Delta H = \frac{2H_0}{(1-\nu)\pi}\int_0^{\pi/2} \frac{\nu - (1-\nu)A\cos X}{1 + A\cos X} dX \quad (2A)$$

where

$$A = \frac{4\nu}{\pi(1-\nu)}\exp\left(-\frac{\pi^2 Dt}{4H_0^2\tau_0}\right)$$

Since $1 >> A\cos X$, Eq. 2A can be written as:

$$\Delta H = \frac{2H_0}{(1-\nu)\pi}\int_0^{\pi/2} [\nu - (1-\nu)A\cos X](1 - A\cos X)dX$$

$$= \frac{2H_0}{(1-\nu)\pi}\int_0^{\pi/2} \nu - A\cos X + (1-\nu)A^2\cos^2 X \, dX \quad (3A)$$

Integrating Eq. 3A, we finally obtain Eq. 4A which is equal to Eq. 12 in the text.

$$\Delta H = \frac{2H_0}{(1-\nu)\pi}\left[\nu\frac{\pi}{2} - A\right] = \frac{\nu H_0}{(1-\nu)}\left[1 - \frac{2A}{\pi\nu}\right] \quad (4A)$$

Derivation of Eq. 16

Substituting Eq. 15 into Eq. 8, we obtain:

$$\Delta H = \int_0^{H_0} \frac{\nu - \nu\tanh\left(\frac{H_0 - x_0}{\sqrt{\pi Dt/\tau_0}}\right)}{(1-\nu) + \nu\tanh\left(\frac{H_0 - x_0}{\sqrt{\pi Dt/\tau_0}}\right)} dx_0 \quad (5A)$$

Changing variable $(H_0 - x_0)/\sqrt{\pi Dt/\tau_0}$ to $-X$, we have $dx_0 = R\,dX$ and:

$$\Delta H = R\int_{-H_0/R}^{0} \frac{\nu - \nu\tanh(-X)}{(1-\nu) + \nu\tanh(-X)} dX \quad (6A)$$

where $R = \sqrt{\pi Dt/\tau_0}$.

Using the relationship $\tanh(-X) = (e^{-x} - e^{x})/(e^{-x} + e^{x})$ and rearranging, we obtain:

$$\Delta H = R\int_{-H_0/R}^{0} \frac{2\nu}{e^{-2x} + (1 - 2\nu)} dX \quad (7A)$$

Using the relationship found in a table of integrals:

$$\int \frac{dx}{a + be^{px}} = \frac{x}{a} - \frac{1}{ap}\log(a + be^{px}) \quad (8A)$$

we obtain:

$$\Delta H = 2\nu R\left[\frac{H_0}{(1-2\nu)R} + \frac{1}{(1-2\nu)2}(\log(2 - 2\nu) - \log(1 - 2\nu + e^{2H_0/R}))\right] \quad (9A)$$

Since $(1 - 2\nu) << e^{2Ho/R}$ and $\log(1 - 2\nu + e^{2Ho/R}) = 2Ho/R$, we finally obtain Eq. 10A which is equal to Eq. 16 in the text.

$$\Delta H = \frac{\nu R \log(2 - 2\nu)}{(1 - 2\nu)} \tag{10A}$$

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