C_{ps}	=	heat capacity of fluidized particles	[kJ/kg K]
De	=	hydraulic diameter	[cm]
D_p	=	particle diameter	[cm]
Dsr	=	lateral diffusion coefficient	[cm^2/s]
D_t	=	tube diameter	[cm]
d_{be}	=	effective diameter of bubble	[cm]
Ke	=	lateral effective thermal conductivity	[KJ/kg·m·K]
L_f	=	bed height at fluidized gas velocity	[cm]
L_H	=	lateral length of fluidized bed	[cm]
Lmf	=	bed height at minimum fluidized gas velocity	[cm]
L_1	=	lateral length in fluidized bed from left wall to partition plate	[cm]
$m1$	=	number of tube in wide direction	[—]
$m2$	=	number of tube in lateral direction	[—]
$m3$	=	number of tube in axial direction	[—]
Q	=	amount of particles moved in lateral direction per unit height	[cm^3/s]
q	=	amount of particles moved in lateral direction when a single bubble passes through the compartment	[cm^3]
U	=	fluidized gas velocity	[cm/s]
Umf	=	minimum fluidized gas velocity	[cm/s]
X	=	lateral distance from left wall of fluidized bed	[cm]
α	=	thermal diffusivity	[cm^2/s]
β	=	proportional constant	[cm/s]
ε_f	=	void fraction at fluidized conditions	[—]
ε_{mf}	=	void fraction at minimum fluidizing conditions	[—]
ρ_b	=	bulk density of fluidized particles	[g/cm^3]
ρ_p	=	density of particles	[g/cm^3]
θ	=	elapsed time	[s]
ϕ_s	=	sphericity of fluidized particle	[—]

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EFFECT OF SYSTEM AGING ON RELEASE PROFILE OF RESERVOIR-TYPE DRUG DELIVERY SYSTEM

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Key Words: Controlled Release, Membrane Transport, Drug Delivery System, Time-Lag, Bursting, Solicone Membrane, 17α-Methyltestosterone

Introduction

The transient characteristics of drug release from a reservoir-type drug delivery system is of importance in the optimum design of controlled-release products. If the drug delivery system is applied shortly after manufacturing, a significant time-lag may be observed before constant release is achieved because the drug molecules do not exist in the fresh rate-controlling membrane initially. When the delivery system has been stored for a while, the drug molecules gradually penetrate into the rate-controlling membrane. And, finally, after a certain period of storage, the drug delivery system will show a typical bursting release due to the release of drug molecules already saturated in the membrane into its surroundings.[5] Since the time-dependent release rate observed initially for the reservoir-type drug delivery system is markedly influenced by the concentration profile of a drug inside the rate-controlling membrane prior to the onset of release, the aging (storage or history) of the drug delivery system should be carefully controlled. With an appropriate aging period, both the time-lag and bursting release could be minimized.

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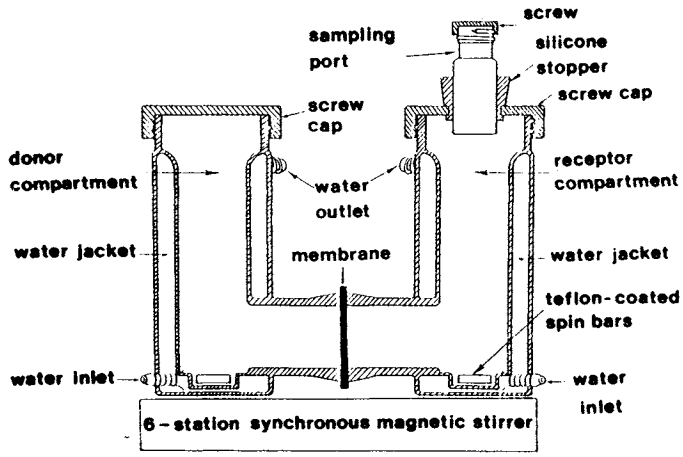


Fig. 1. *In vitro* membrane permeation system. Membrane = silicone elastomer (PDMS with filler, 0.10 cm in thickness with effective surface area of 13.9 cm^2). Magnet (length = 2.54 cm; rotation speed at 425 rpm). Volume of each compartment = 170 ml.

The effect of initial concentration profiles on the transient release rate from the reservoir-type drug delivery system was analyzed numerically.[4] Both the time-lag and bursting release were found to be minimized by controlling the initial concentration profile in the rate-controlling membrane.

In the present study, experiments were developed to investigate the effect of the aging period on the transient permeation profile of a drug through a silicone membrane using a well-calibrated membrane permeation system.[6]

Experimental

The membrane permeation system used in the present study is shown in **Fig. 1**. An excess amount of 17α-methyl-testosterone solid crystals was suspended in an aqueous solution containing 40% v/v of polyethylene glycol 400, 170 ml of which was placed in the donor compartment. Excess solid drug was added to assure that the solution remained at a constant equilibrium drug concentration throughout the experiment. The co-solvent, PEG400, was used as a solubilizer to enhance the drug solubility and to maintain the sink condition required. The effect of PEG400 on the solubility of the drug is shown in **Fig. 2**. After exposing only the donor side of the membrane to the drug solution for various aging periods (0, 6.5, 10, 15, 20, 31, 46, 82 h), an equal volume of the same aqueous solution containing no drug was charged into the receptor compartment. Both the donor and the receptor solutions were agitated by a pair of bar-shaped magnets rotating at a synchronous 425 rpm. Under these conditions, the effect of the diffusion boundary layer on the rate of drug permeation was found to be negligible and the sink condition was also maintained.[6] The temperature in the membrane permeation system was controlled at 37 ± 0.2°C using a circulating water bath. A medical-

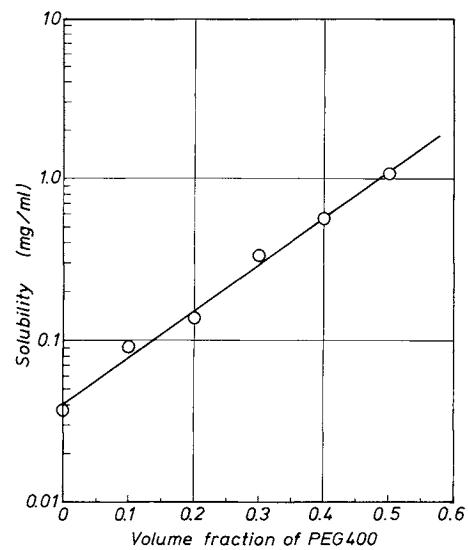


Fig. 2. Effect of polyethylene glycol 400 (volume fraction) on solution solubility of 17α-methyltestosterone.

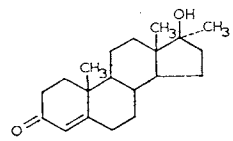
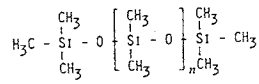
grade silicone membrane (polydimethylsiloxane with filler, 0.10 cm in thickness) was used as a rate-controlling membrane. Important physical properties of the present experimental system are listed in **Table 1**.

At the time intervals mentioned above, ten ml of the receptor solution was withdrawn and, quickly, an equivalent volume of the fresh solution was added to maintain the same solution volume in the receptor compartment. The drug concentration in the samples taken was then analyzed using a UV/VIS spectrophotometer (Perkin-Elmer model 559A).

Results and Discussion

The cumulative amount Q of drug permeated through the membrane is plotted in **Fig. 3** as a function of time. It is interesting to observe that the time-lag, which is defined as the intercept of the Q versus

Table 1. Physicochemical properties of the drug/solution system at 37°C

Chemical structure:	
17α-Methyltestosterone (M.W. 302.5)	
Silicone membrane: (PDMS without filler)	
Membrane thickness	0.10 cm
Solubility of 17α-methyltestosterone:	
in 40% PEG400	0.559 mg/ml
in silicone fluid (DC360, 20 cP)	0.238 mg/ml
Viscosity of 40% PEG400 solution	0.046 Pa·s
Density of 40% PEG400 solution	1.047 g/ml
Drug diffusivity in 40% PEG400	0.98×10^{-6} cm^3/s

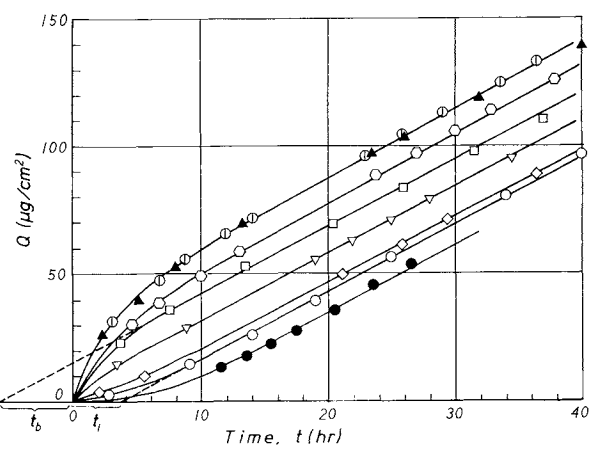


Fig. 3. Permeation profile of 17α-methyltestosterone as a function of time after various aging periods: (●) 0 hr; (○) 6.5 hr; (◇) 10 hr; (▽) 15 hr; (□) 20 hr; (○) 31 hr; (▲) 46 hr; (ⓘ) 82 hr.

time line on time axis, is clearly influenced by the aging period of the membrane. The time-lags determined from the Q versus time plots (Fig. 3) are found to be a function of the aging time in **Fig. 4**. As can be seen, the time-lag for the fresh membrane ($t_l = 6.0$ h) is exactly one-half the bursting time ($t_b = 12.0$ h) and this finding agreed well with the theoretical calculation.[1,3] From the time-lag and bursting time, we can evaluated the drug diffusivity D through the present silicone membrane (thickness $l = 0.10$ cm):

$$D = \frac{l^2}{3t_b} = \frac{l^2}{6t_l} = 0.772 \times 10^{-7}\ \text{cm}^2/\text{s} \qquad (1)$$

The diffusivity of the present drug is the same order of magnitude for progesterone diffusivity reported earlier.[2,5] Figure 4 also indicates that the optimum aging time, at which neither time-lag nor bursting

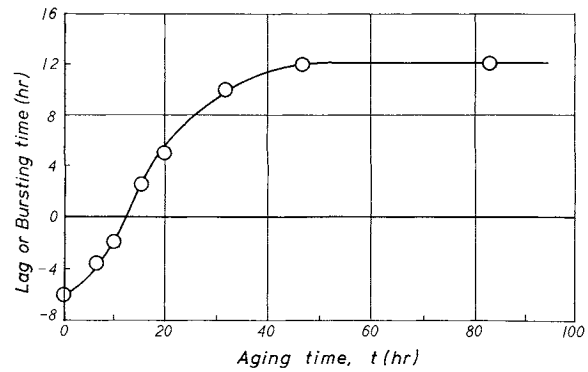


Fig. 4. Effect of aging period on time-lag or bursting time.

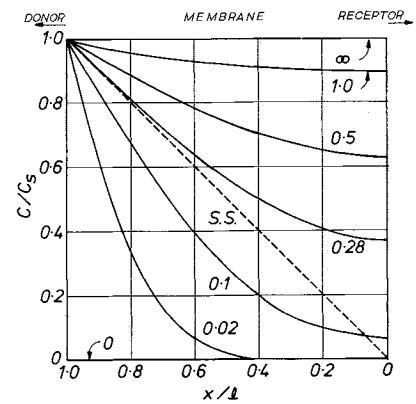


Fig. 5. Initial concentration profile of drug in the membrane (Eq. 2). Numbers on curves are dimensionless aging time θ ($= Dt/l^2$); ----, steady-state concentration profile.

was observed, was about 11 h for the present drug/membrane system.

The concentration profile in the membrane during the initial phase of the aging period can be given, theoretically, by the following equation[3]:

$$\frac{C}{C_s} = 1 - \frac{4}{\pi} \sum_{n=0}^{\infty} \frac{(-1)^n}{2n+1} \exp\left\{-D(2n+1)^2\pi^2 t/4l^2\right\} \times \cos\frac{(2n+1)\pi x}{2l} \qquad (2)$$

where C_s, t and x are the saturated drug concentration in the membrane, the time of storage period, and the distance from the membrane-receptor boundary (**Fig. 5**), respectively.

The dimensionless concentration gradient at $x = l$ (donor side) is then given by

$$\left.\frac{d(C/C_s)}{d(x/l)}\right|_{x=l} = 2 \sum_{n=0}^{\infty} \exp\left\{-\frac{(2n+1)^2\pi^2}{4}\frac{Dt}{l^2}\right\} \qquad (3)$$

At steady state, the dimensionless concentration gradient becomes unity because no diffusion boundary layer existing on the surface of the membrane is assumed.

The time at which the initial concentration gradient at $x = l$ reaches the same concentration gradient as

that under the steady-state condition can be calculated:

$$\sum_{n=0}^{\infty} \exp\left\{-\frac{(2n+1)^2\pi^2}{4}\frac{Dt}{l^2}\right\}=0.50$$

$$\theta=\frac{Dt}{l^2}=0.28 \quad \text{or} \quad t=10.5\,\text{h} \qquad (4)$$

The aging time calculated agrees fairly well with the experimental results. It can be concluded that the optimum aging time to minimize both the time-lag and the bursting release from the reservoir-type drug delivery system can be considered approximately as the time at which the flux of drug permeation from the inner surface of the membrane becomes identical to that under the steady-state condition. If the storage period of the drug delivery system is longer than the optimum aging period determined from Eq. (4), the initial release must be carefully examined before application in order to avoid any possible side effect caused by bursting release.

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Nomenclature

C = drug concentration in membrane
C_s = saturated drug concentration in membrane or saturated drug concentration in donor compartment with partition coefficient of one
D = drug diffusivity in polymer membrane
l = membrane thickness
Q = cumulative amount of drug permeated
t = time
t_1 = time lag (Fig. 3)
t_b = bursting time (Fig. 3)
x = distance from surface of membrane (Fig. 3)
θ = dimensionless time defined by Dt/l^2
π = 3.14156

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A DYNAMIC CHARACTERIZATION OF FLUIDITY FOR GAS-SOLID FLUIDIZATION

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Key Words: Fluidization, Chemical Reactor, Fluidized Bed, Fluidity, Sedimentation

Gas-solid fluidized beds show various fluidizing states depending on the properties of gas and solid particles, operating conditions and characteristics of equipment. Geldart[2] classified solid particles into four groups A, B, C and D by the average size of solid particles and the density difference between gas and solid particles. With group A particles, bubbles begin to evolve at a gas velocity higher than the minimum fluidization velocity, and the rate of bubble growth is rather limited. With group B particles, bubble formation begins at the minimum fluidization velocity, and bubble size increases with increasing height above the distributor. Group C and D particles are not easily fluidized.

Abrahamsen *et al.*[1] studied the effect of the properties of gas and solid particles on the ratio of minimum bubbling velocity to minimum fluidization velocity, and used this ratio as the criterion between groups A and B. Molerus *et al.*[4] interpreted Geldart's classification by taking the interparticle cohesive forces into consideration, while Rietema[7] arranged the classification by the concept of the elasticity modulus. Yasui *et al.*[8] evaluated the fluidity of Geldart's group A particles by plotting gas holdup data on the re-

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