CONTROLLED RELEASE OF LOCAL ANESTHETICS

THROUGH POLYMER MEMBRANES

by

Kazuhiko Juni

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INTRODUCTION

Recently, much effort has been centered in increasing the effectiveness and decreasing side-effects of drugs in therapy. On that standpoint, a number of drug delivery systems have been designed and examined to improve drug therapy over that achieved with conventional preparations[1-19].

An effective therapy is better achieved by the attainment of the appropriate concentration of drug at the particular target site within the body for a desired duration. When a drug is administered to a patient, it must be transported from the site of administration to a target site. Therefore, the route of administration as well as the dose of drug becomes important factor in governing therapeutic actions.

Some typical examples are schematically shown in Fig. 1, a. The ordinate shows drug level in plasma or corresponding drug level in particular tissue. When a drug is administered intravenously, orally, or intramuscularly, drug level decreases exponentially with time after its peak level. Administration of large doses, although drug levels can be maintained in the therapeutic range for longer periods of time, may result in a toxic effect. Repeated dosing has been adopted to achieve longer duration of drug action (Fig. 1, b). As is apparent in the figure, inadequate dosing intervals may cause insufficient drug levels (because of too long intervals) or toxic reactions (too short intervals). Patient compliance with the dosing regimen may limit the success in the repeated dosing therapy.

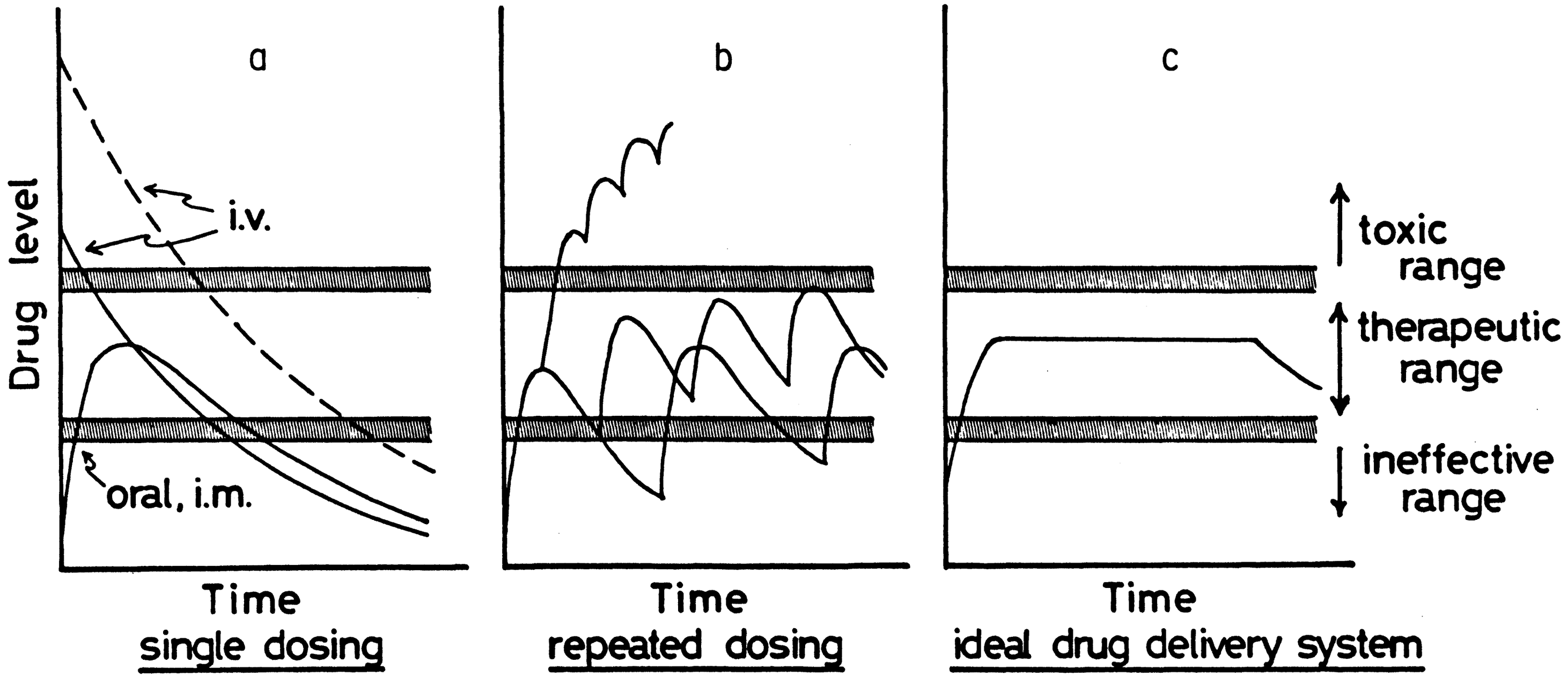

Figure 1. Typical Drug Level Versus Time Profiles for Several Dosing Manners

An ideal drug delivery system may be described as follows: the system contains and releases a minimum amount of drug sufficient to maintain the therapeutic action at the target for a desired period of time (Fig. 1, c). Thus, incidences of side reactions, concentration-dependent or site-dependent, could also be minimized. Such an ideal system has not yet been prepared and further development is desired.

A controlled-release formulation or delivery system contains drug in polymeric material and can allow drug delivery to the target organ at controlled rates over a specified period. One form of these system is a capsule of polymeric material filled with the drug in a fluid. The role of membrane in controlling the release rate of drug is well known. Since permeation is a three-step process of partition into, diffusion through, and partition out of the membrane, the permeation rate of drug depends on the nature of the membrane materials as well as the thickness and area of the membrane. Thus, the choice of membrane materials is important[20,21].

Besides the membrane, the design of the drug reservoir can influence the drug release characteristics. If simple solutions of drug are enclosed within the membrane, the drug permeation rate declines rapidly unless the reservoir volume is large. In order to design the reservoir with a limited volume but of large sustaining capacity, suspensions have been employed as the reservoir system[22]. Since suspensions have their own problems such as sedimentation and particle-size growth of the dispersed drug during storage which may cause an unprogrammable release

rate of drug, a reservoir in the form of a solution is sometimes preferred.

In this work, possible uses of complexes, micelles, cosolvents, and emulsions in sustaining the release of drug were proposed. By using these systems, the drug can be introduced in a solubilized form. The functionality of each system as a reservoir was examined.

It is reported that , in patients with advanced cancer, pain becomes their main complaint during their last year of life[23]. Once causal treatment is no longer able to cure the patient, the main goal of further therapy is the comfort of the patient.

In order to relieve these patients from unbearable pain, local anesthetics are often administered. In this work, means of controlling release of local anesthetics are examined because of great demand of achieving an extended period of anesthetic action from clinicians operating pain clinics. The present approaches can however be extended to controlled release of other therapeutic agents such as steroids and anticancer agents.

THEORETICAL CONSIDERATIONS
(WITH LITERATURE REVIEW)

1. Drug Release through Polymer Membranes and Polymer Matrices[22,24]

When the transfer of drug through a polymer membrane from a donor solution to a receptor solution is considered, Fick's law of diffusion can be restated:

$$\frac{dMr}{dt} = -DA \frac{dCm}{dx} \qquad \text{(Eq. 1)}$$

where dMr/dt = release rate, D = diffusivity in the membrane, A = surface area of the membrane, and dCm/dx = concentration gradient in the membrane.

In the steady state, Eq. 1 may be written:

$$\frac{dMr}{dt} = DA \frac{Cm,d - Cm,r}{\ell} = DA \frac{KdCd - KrCr}{\ell} \qquad \text{(Eq. 2)}$$

where Cm,d and Cm,r = drug concentrations in the membrane at the donor side and receptor side, respectively; Kd and Kr = distribution coefficients of the drug between the membrane and donor solution and the membrane and the receptor solution, respectively; Cd and Cr = drug concentrations in the donor solution and the receptor solution, respectively; and ℓ = thickness of the membrane.

If a sink condition is maintained in the receptor solution, Cr remains negligible compared to Cd. Then Eq. 2 can be simplified to:

$$\frac{dMr}{dt} = \frac{DAKd}{\ell} Cd = \frac{AP}{\ell} Cd \qquad \text{(Eq. 3)}$$

where P = Dkd = permeability.

When an undersaturated drug solution (or a saturated drug solution without excess solid phase) is placed in the donor compartment, the drug concentration in the donor solution decreases with time as the drug permeates to the receptor solution (Fig. 2, a). Under this condition, Eq. 3 becomes:

$$\frac{dMr}{dt} = \frac{AP}{\ell} C_d^i \exp(-APt/\ell V) \qquad \text{(Eq. 4)}$$

where V = volume of the donor solution and C_d^i = initial concentration of drug in the donor solution. Thus, the release rate decreases exponentially with time.

When a drug is dispersed as a solid in a polymer matrix (Fig. 2, b), the release equation has been derived by T. Higuchi[25].

$$\frac{dMr}{dt} = \frac{A}{2}\left[\frac{DC_s^m}{t}(2C_0 - C_s^m)\right]^{1/2} \qquad \text{(Eq. 5)}$$

$$\simeq \frac{A}{2}\left[\frac{2DC_s^m C_0}{t}\right]^{1/2} \text{ for } C_0 \gg C_s^m \,. \qquad \text{(Eq. 6)}$$

where C_s^m = solubility of drug in the polymer phase and C_0 = total concentration of drug in the matrix (dissolved plus dispersed). The assumption that $C_0 \gg C_s^m$ is reasonable for polymer-drug dispersions containing more than 5 wt% drug, but it is often valid for polymer-drug dispersions containing as little as 1 wt% drug[22]. From Eq. 5 it follows that the release rate is inversely proportional to the square root of time, meaning that the release rate decreases with time.

In order to achieve constant release from a drug delivery system, the concentration gradient has to be maintained constant.

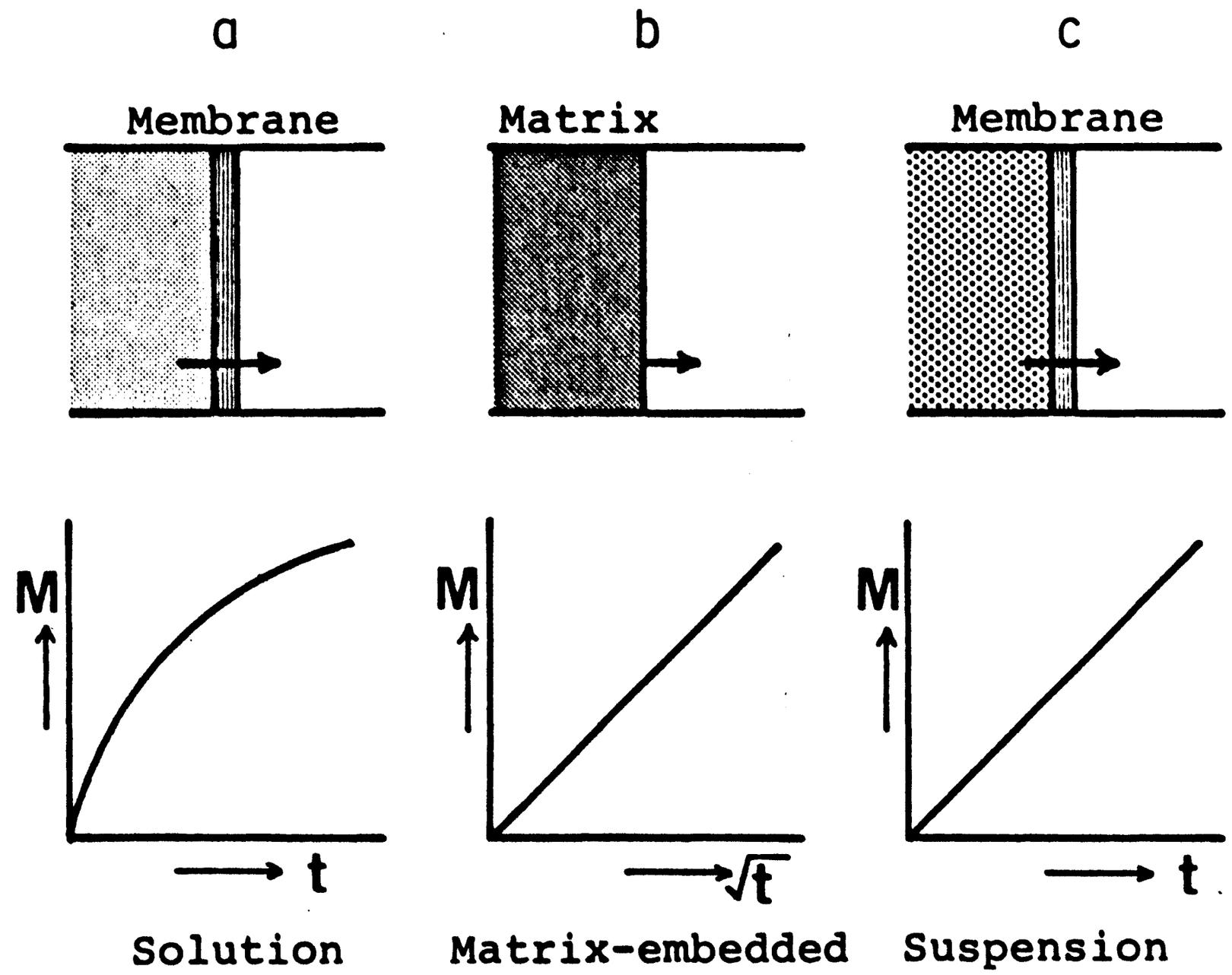

Figure 2. Release Patterns of Drug in Three Cases

A constant concentration gradient may be achieved by having either: a) a large volume reservoir of drug in the solution[26] or b) the drug in the solid phase[22] in the donor side of a membrane and a sink condition in the receptor side. Because of the difficulty in accomodating a large volume reservoir within the drug delivery system, suspensions are usually employed to maintain the drug concentration within the delivery system constant.

When a suspension is placed at the donor side (Fig. 2, c and Fig. 3, a), the drug concentration in the donor solution remains constant because loss of drug from the solution by permeation is constantly compensated for by the dissolution of solid drug. Eq. 3 is then written:

$$\frac{dMr}{dt} = \frac{AP}{\ell} Cs \qquad \text{(Eq. 7)}$$

where Cs = solubility of the drug in the donor solution. Since all terms on the right-hand side of Eq. 7 are constant, the release rate of drug through the membrane is constant.

When a drug-dispersed matrix is laminated by a polymer membrane with smaller permeability, a core matrix serves as a reservoir for the release. Constant release rates of drugs have been obtained by such lamination[27].

A new approach to obtain constant-rate release of drug from drug-dispersed matrix was described[28,29]. The system, having an unique geometry, was theoretically analyzed and experimentally tested for its drug-releasing behavior. This principle was also applicable to release of drug from the solid drug.

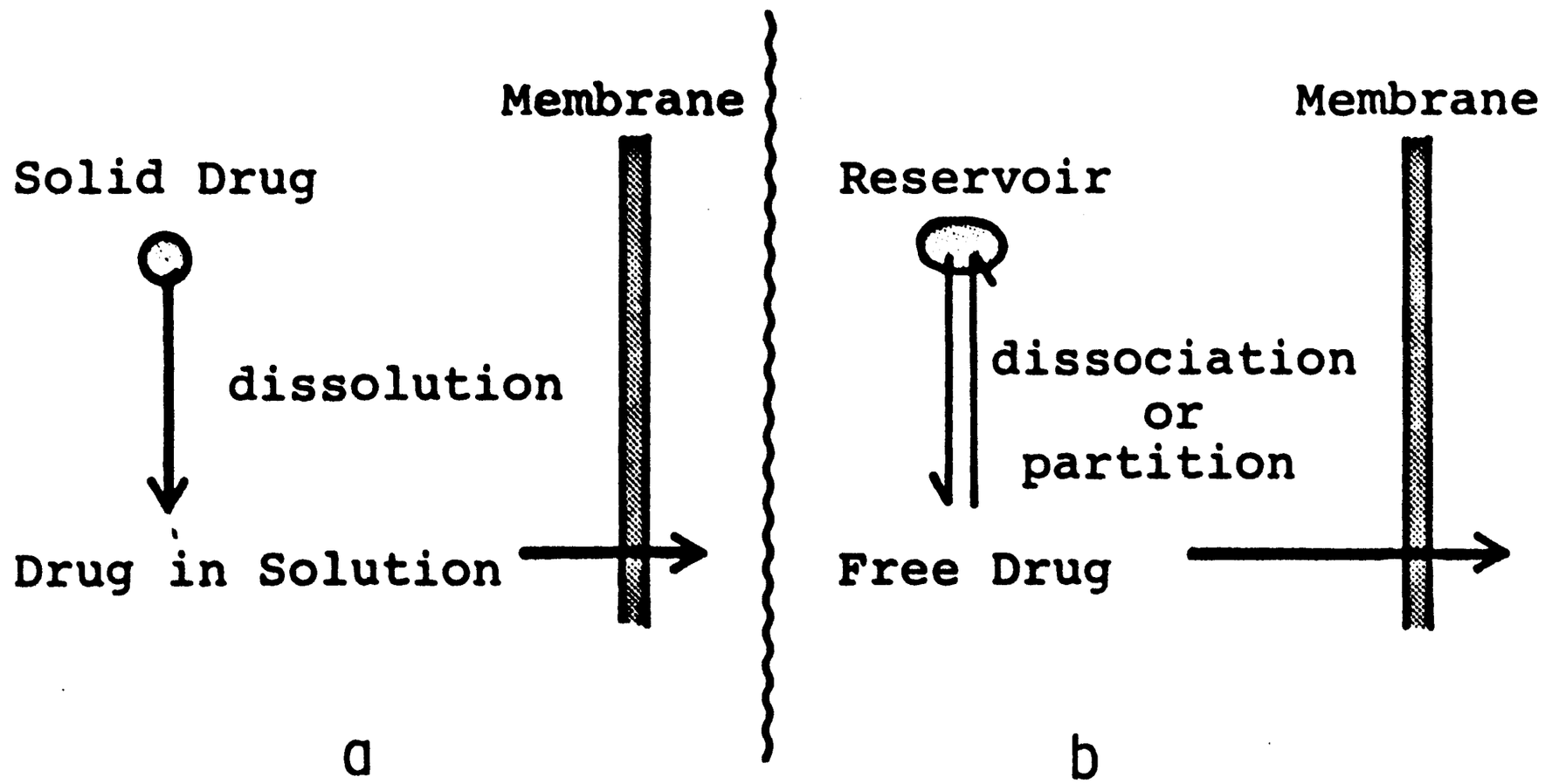

Figure 3. **Mechanisms in Sustained-Release of Drug for Suspension and The Proposed Reservoir Systems**

2. Systems Containing Soluble Complexes[24,30)]

Complexation in pharmaceutical systems has been studied by many workers[31)]. Its possible role in accelerating or retarding drug permeation through a silicone membrane has been reported [32,33)]. When a drug solution containing a complexing agent is placed in the donor compartment, the complexed drug may serve as a reservoir (Fig. 3, b). Loss of uncomplexed (permeable) drug from the donor solution by permeation is partly compensated for by dissociation of the complex. Therefore, the concentration of permeable drug does not decrease as rapidly as in the plain solution (Fig. 2, a).

When the fraction of complexed drug is large, the concentration of permeable drug may be kept fairly constant and the release rate declines only slowly. Dissociation of drug from the complex is a very rapid process[34,35)] compared to the diffusion process in the membrane. Therefore, the following assumptions seem to be reasonable that an equilibration between the free drugs and complexes is established at any moment and that diffusion in the membrane is a rate-limiting process in the drug release.

In the present studies, the effects of three types of complexes on the permeation of a local anesthetic were investigated. The complexes included were: a) plane to plane, b) inclusion, and c) macromolecular complexes. Caffeine has been reported to form complexes with aromatic molecules, presumably of plane-to-plane stacking[36-38)]. α- and β-Cyclodextrins, on the other hand, have been known to include drug molecules within their cavities[39-43)].

Povidone, a water-soluble polymer, has been studied as to its complexing tendencies with drugs[44]. 7-(2-Hydroxyethyl)theophylline is also expected to form complexes with aromatic molecules.

3. Systems Containing Micelles[30,45,46]

Surfactants in aqueous solution are known, above their critical concentrations, to form micelles into which the drug can partition[47]. The drug solubilized in the micelles, in turn, can partition back into the bulk solution when the drug concentration in the bulk phase is decreased due to permeation through a membrane (Fig. 3, b).

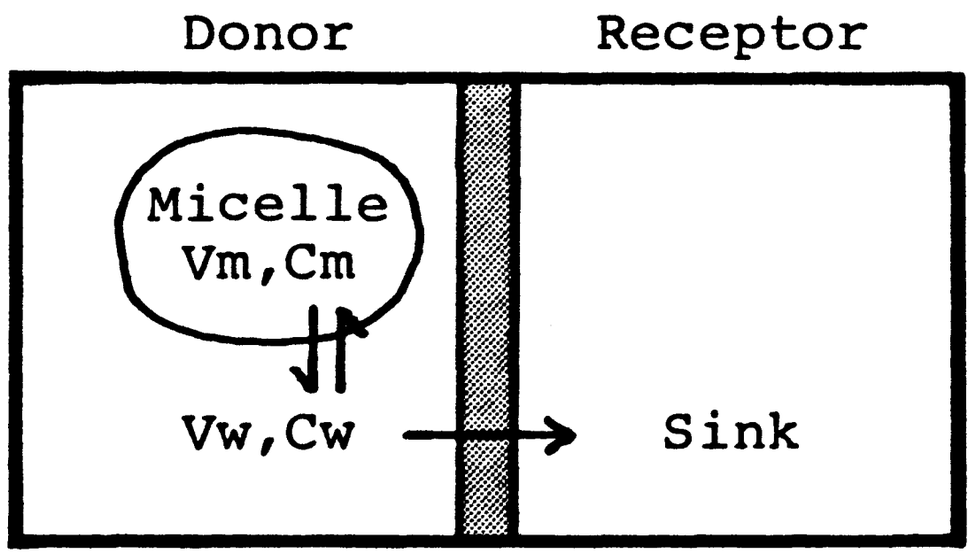

Figure 4. Schematic representation of sustained release of drug from a system containing micelles (proposed model).

For this system, the following simple model shown in Fig. 4 is considered: 1) in the donor compartment, the drug is distributed between the two phases, i.e. a dispersed micellar phase and a continuous aqueous phase and only the drug in the latter can permeate through the membrane, 2) distribution of the drug between the micellar and aqueous phases is instantaneous at any moment, and 3) contribution of the diffusion layer effect at the membrane surface can be neglected.

The distribution coefficient, Kp of the drug between these two phases is given by:

$$Kp = \frac{Cm}{Cw} = \frac{Mm/Vm}{Mw/Vw} \qquad \text{(Eq. 8)}$$

where C, M, and V denote the concentration and the amount of the drug in each phase, and the volume of each phase, respectively, and the subscripts m and w indicate a micellar phase and an aqueous phase, respectively. Under these conditions, if sink conditions are maintained in the receptor side, Eq. 3 becomes:

$$\frac{dMr}{dt} = \frac{APCw}{\ell} \qquad \text{(Eq. 9)}$$

where Mr = the amount of drug in the receptor solution at time t. The total amount of drug in the donor solution, Mt is given by:

$$Mt = Mm + Mw = M_\infty - Mr \qquad \text{(Eq. 10)}$$

where M_∞ = the total amount of drug initially introduced into the system. Rearrangement of Eq. 8-10 leads to:

$$Mr = M_\infty \left[1 - \exp\left\{- \frac{APt}{\ell(Kp \cdot Vm + Vw)}\right\}\right] \qquad \text{(Eq. 11)}$$

By definition:

$$M_\infty = VmCm^0 + VwCw^0 \qquad \text{(Eq. 12)}$$

$$Cm^0 = KpCw^0 \qquad \text{(Eq. 13)}$$

where Cm^0 and Cw^0 are the initial concentrations of drug in the micellar phase and aqueous phase, respectively. Rearrangement of Eq. 11-13 leads to Eq. 14.

$$Mr = M_\infty\left\{1 - \exp(-APCw^0 t/\ell VCt^0)\right\} \qquad \text{(Eq. 14)}$$

where V = the volume of the donor solution and Ct^0 = the total initial concentration of drug in the donor solution. The ratio Cw^0/Ct^0 is equal to Cs^0/Cs at equilibrium, where Cs^0 and Cs = the solubilities of drug in water and a surfactant solution, respectively. Then, Eq. 14 becomes:

$$Mr = M_\infty\left\{1 - \exp(-APCs^0 t/\ell VCs)\right\} \qquad \text{(Eq. 15)}$$

or in rewritten form:

$$-\ln\left(1 - \frac{Mr}{M_\infty}\right) = \frac{APCs^0}{\ell VCs} t \qquad \text{(Eq. 16)}$$

For the system where a drug solution is enclosed in the hollow cylinder, Eq. 17 has been reported[48]:

$$Mr = M_\infty\left[1 - \exp\left\{-2\pi hPt/V\ln(r_o/r_i)\right\}\right] \qquad \text{(Eq. 17)}$$

where r_i and r_o = inner and outer diameters of the cylinder and h = the length of the cylinder. For the case where a drug solution containing micelles, Eq. 18 was derived following the same manner as was done in deriving Eq. 15 from Eq. 3:

$$Mr = M_\infty\left[1 - \exp\left\{-2\pi hPCs^0 t/V\ln(r_o/r_i)Cs\right\}\right] \qquad \text{(Eq. 18)}$$

4. Systems Consisted of Cosolvents[46)]

The solubility of a drug that is insoluble in a particular solvent can usually be increased significantly by the addition of a cosolvent in which the drug is more soluble. The vehicle (solvent mixture), having the ability to retain much drug, can be considered to serve as a large reservoir of the drug.

It has been shown that for a large number of binary aqueous solvent systems, the logarithm of the solubility of various drugs is directly proportional to the fraction of a cosolvent when the polarity of the drug is significantly less than that of either solvent[49-51)]. The relation is expressed as follows:

$$\log Cs' = \log Cs^0 + \sigma f \qquad \text{(Eq. 19)}$$

where Cs' and Cs^0 = the solubilities of drug in the solvent mixtures and that in pure water, respectively, σ = a constant which is related to the solubilizing power of the cosolvent for the drug, and f = the fraction of cosolvent.

The drug release through a partition membrane from systems consisted of cosolvents was considered. In the case where drug diffusion in the membrane is the rate-limiting step and a sink condition is maintained in the receptor solution, as defined previously:

$$P_0 = D_0K_0 \qquad \text{(Eq. 20)}$$

when the donor solution is an aqueous solution, and

$$P' = D'K' \qquad \text{(Eq. 21)}$$

when the donor solution is a mixed solvent, where P_0, D_0, and K_0 are the permeability, diffusivity in the membrane, and distribution coefficient of the drug between the membrane and donor solution, respectively, for the aqueous solution system, and P', D', and K' are those for the cosolvent system, respectively. Assuming that the diffusivity in the membrane is not affected by the composition of the donor solution, Eq. 21 becomes:

$$P' = D_0 K' \qquad \text{(Eq. 22)}$$

Distribution coefficient can be expressed in terms of solubility:

$$K_0 = \frac{Cs^m}{Cs^0} \qquad \text{(Eq. 23)}$$

and

$$K' = \frac{Cs^m}{Cs'} \qquad \text{(Eq. 24)}$$

where Cs^0, Cs', and Cs^m are the solubilities of drug in water, a mixed solvent, and a membrane, respectively. From Eqs. 19-24, P' is given by:

$$P' = P_0 \cdot 10^{-\sigma f} \qquad \text{(Eq. 25)}$$

Then, an equation which may describe the release profile of drug through a partition membrane from systems consisted of cosolvents is derived from Eq. 4 and Eq. 25:

$$\frac{dMr}{dt} = \frac{AP \cdot 10^{-\sigma f} Cd^i}{\ell} \exp(-AP \cdot 10^{-\sigma f} t/\ell V) \qquad \text{(Eq. 26)}$$

or

$$Mr = M_\infty \left\{ 1 - \exp(-AP \cdot 10^{-\sigma f} t/\ell V) \right\} \qquad \text{(Eq. 27)}$$

where M_∞ = the amount of drug originally introduced into the system. Similarly, Eq. 28 can be derived from Eq. 17 and Eq. 25 for hollow cylinders:

$$Mr = M_\infty \left[1 - \exp\left\{-2\pi hP \cdot 10^{-\sigma f} t/V \ln(r_o/r_i)\right\}\right] \quad \text{(Eq. 28)}$$

In the present investigations, macrogol(polyethylene glycol) 400 was selected as a cosolvent, and the macrogol-water mixtures of various fractions were evaluated as to their drug release-sustaining behavior.

5. Systems Consisted of Oil-in-Water Type Emulsions[46)]

An oil-in-water type emulsion is also expected to serve as a reservoir for the drug with considerable lipophilicity. When an emulsion of that sort which contains the drug mainly in its oil phase (because of high lipid solubility of the drug) was applied to the drug release system, sustained release of the drug may be achieved. The mechanism can be considered similarly to that described in the micellar system (Fig. 3, b and Fig. 4). Loss of drug in an aqueous phase in the donor medium due to permeation can be partly compensated for by partition of the drug from an oil phase to the aqueous phase.

Emulsions are widely used in pharmaceutical preparations. An emulsion, in its nature, is a thermodynamically unstable system, i.e. fine droplets of oil are dispersed in a continuous aqueous phase. Therefore, coalescence or flocculation inevitably occurs among the dispersed phases due to the natural tendency of like molecules to coalesce.

Various information for the stability of emulsions has been reported[52,53)] in which the effects of temperature, oil fractions, concentrations of emulsifiers, or many other factors on the emulsion stability are examined. The stabilization of the system has been under challenging. If properties and/or phase composition of the components of the system do change during the use, the release behavior of the drug may be affected when emulsions are applied to the drug release system.

EXPERIMENTAL

1. Hydrolysis Studies

The rates of hydrolysis of benzocaine and butamben in 0.05N NaOH solutions were followed in a constant temperature cell at 30°. Initial concentrations of each drug were 1/50 of their respective solubilities at 30°. Ultraviolet (UV) spectra were repeatedly scanned at intervals of 10 min to follow their changes with time due to hydrolytic breakdown employing a double-beam recording spectrophotometer. The percentage of the intact (unhydrolyzed) drug was calculated from the absorbance of the reaction solution using the absorptivity values for benzocaine, butamben, and their hydrolytic product, p-aminobenzoic acid.

2. Solubility Studies

An excess amount of butamben was placed into each vial containing a complexing agent, surfactant, or cosolvent at various concentrations. The vials were immersed in a bath maintained at constant temperature (30.0 ± 0.5° or 37.0 ± 0.5°) and the contents were equilibrated by shaking or by stirring magnetically for at least 24 hours. In the β-cyclodextrin system, where a complex with limited solubility was formed, or in the system which gave high butamben solubility, a longer equilibration period (2 to 3 days) was required. Equilibrated mixtures were then filtered quickly through a sintered-glass disk, and after appropriate dilution with distilled water, samples were assayed for butamben contents. In the cosolvent systems, filtered samples were diluted with ethanol to avoid possible precipitation of butamben[54]. Analytical methods were as follows.

Spectrophotometric Assay --- In the absence of any interfering material, the UV absorbance of butamben at 287 nm (λ_{max} in aqueous solution) or at 295 nm (λ_{max} in ethanol) was used to determine the concentration of butamben in the sample.

In the presence of 7-(2-hydroxyethyl)theophylline, which shows its λ_{max} at 272 nm in the aqueous solution and interferes with UV assay for butamben, the solubilities of butamben were measured by means of dual-wavelength UV spectrophotometry at the following two wavelengths, λ_1 = 258 nm and λ_2 = 285 nm.

GLC Assay --- Caffeine also interferes with UV assay for butamben because it shows its λ_{max} at 272 nm in aqueous solutions. Concentrations of butamben in solutions containing caffeine were determined by GLC. A known amount of benzocaine (as internal standard) was added to a sample solution, and water was vacuum evaporated. The residue was subsequently dissolved in 50µl of chloroform, and a 2-µl portion of the chloroform solution was injected into the column.

GLC conditions were as follows: apparatus, gas chromatograph with a flame ionization detector; column, 2-m stainless steel with 1.5% OV-101 on Shimalite W (80 - 100 mesh); injection port temperature, 173°; detector temperature, 275°; nitrogen (carrier gas) flow rate, 30 ml/min; hydrogen flow rate, 25 ml/min; and air flow rate, 940 ml/min. The retention times for benzocaine (as internal standard), butamben, and caffeine were 1.9, 3.6, and 4.3 min, respectively.

3. Release Studies In Vitro

3-1 Preparation of Test Solutions of the Drugs

Drug Suspensions --- A known excess amount of drug was added to distilled water with or without suspending agent or surfactant in flask, and the content was then vigorously agitated to effect better dispersion of drug particles for at least 10 hours at the temperature.

Drug Solutions --- A calculated amount of drug was added to a solution containing each vehicle and dissolved completely. In order to obtain saturated drug solutions, the same procedures as in solubility studies were used except for larger volume of solutions. Equilibrated mixtures were filtered just prior to permeation experiments.

Emulsions --- An oil-in-water type emulsion was prepared in the following procedure. A weighed amount of butamben was initially dissolved in cotton seed oil. The oil solution was then poured into the aqueous sodium alginate solution containing a small amount of polysorbate 80 with stirring. An ultrasonic vibrator was used to emulsify the oil in water at 100 watts for 30 sec. The emulsion thus formulated was found to be of an oil-in-water type as determined by the dilution method and the dye-solubility test.

3-2 Evaluation of Emulsion Stability

To examine the physical stability of the emulsions, emulsions were prepared using various concentrations (0.5 - 2.0%) of sodium

alginate and various oil fractions (10 - 50%). Emulsions thus prepared were kept standing in test tubes (10-mm diameter) for up to 5 days at room temperature. The emulsions which resulted in phase separation into a supernatant clear phase and a lower turbid phase were regarded as unstable.

3-3 Permeation Experiments Using Diffusion Cells

Three types of diffusion cells were used in this work.

Permeation Experiments Using Diffusion Cell Type 1 --- The quasi-steady-state diffusion cell described by M. Nakano and N.K. Patel[32] was used and is shown schematically in Fig. 5 (Type 1).

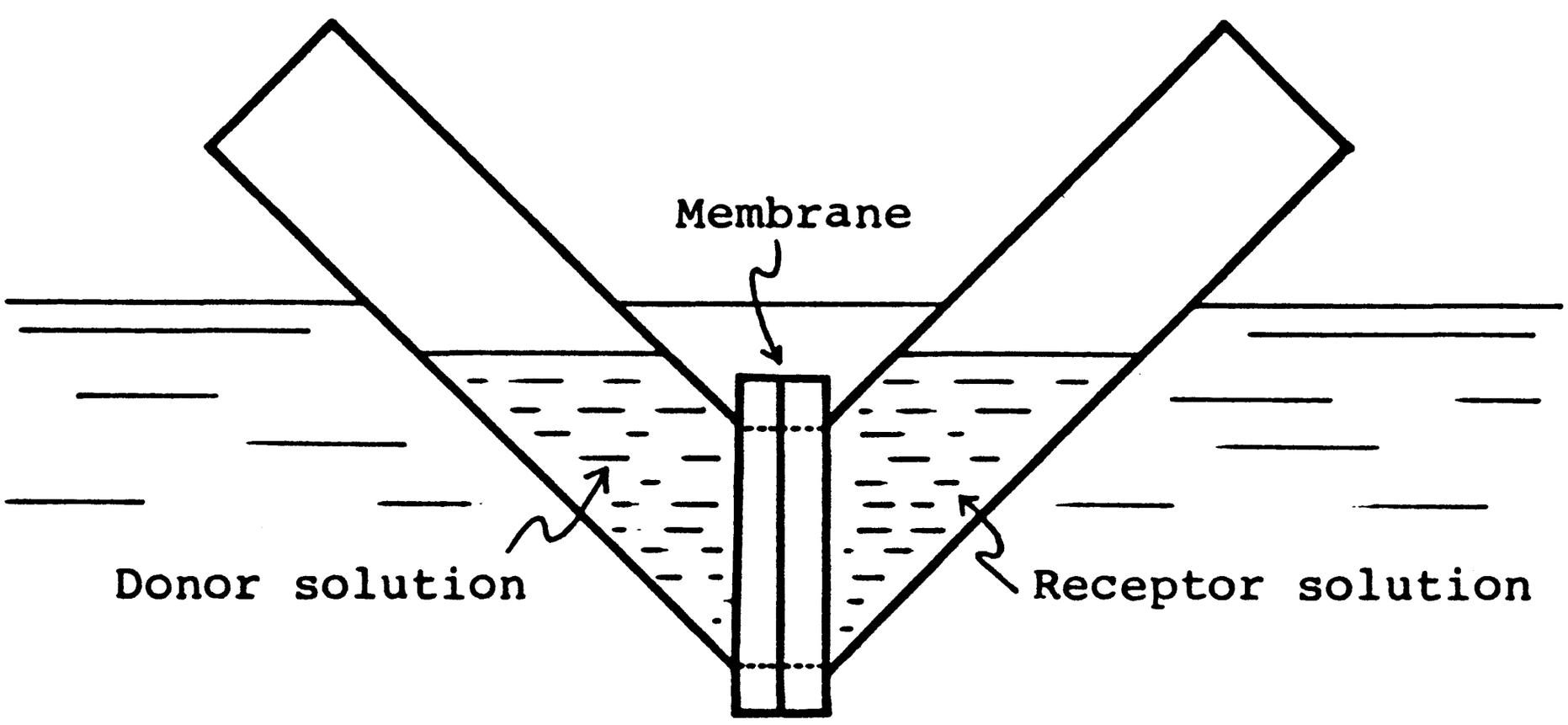

Figure 5. Illustration of the diffusion cell type 1 used in the permeation experiments.

The cell is consisted of two half cells made of stainless steel, a polytetrafluoroethylene O-ring, and a membrane. A silicone membrane and the O-ring were placed between the cell halves, and the halves were joined tightly by nut-and-bolts. The diameter of the membrane area avilable for diffusion was 32 mm.

The cell was initially equilibrated overnight in a shaker bath maintained at 30.0 ± 0.5° with 50 ml of distilled water in both arms. Water was removed by suction; 40 ml of 0.1N HCl solution (to maintain a sink condition with respect to the permeable species in the receptor solution by protonating the permeated drug) was added to one arm, and an equal volume of a test solution was pipetted into another arm. All the solutions were warmed to 30° before being placed into the cell.

The cell was mechanically shaken horizontally at a rate of 70 ± 2 strokes/min. Only in the suspension system in water, instead of shaking the cell itself, the contents of both arms of the cell were stirred with propellers attached to electric motors to effect better dispersion of the solid drug. A 0.5 ml portion of the receptor solution was pipetted out at predetermined time intervals and diluted with pH 6 phosphate buffer. Subsequently UV absorbance of the unprotonated drug was measured at 287 nm.

Permeation Experiments Using Diffusion Cell Type 2 --- The newly designed diffusion apparatus is illustrated in Fig. 6(Type 2)[30]. The glass cell consisted of the donor and receptor compartments (22 mm in inner diameter and 40 mm long in one compartment), and the membrane (available area = 4.52 cm^2) placed between them. The cell was immersed in a jacketed container maintained at 30.0 ± 0.1° by circulating water from the constant temperature bath. The content of each compartment was stirred with a magnetic spin-fin (20 mm in diameter and 15 mm in thickness, Toyo Scientific Products Co., Osaka) which was rotated by a magnet attached to an electric motor.

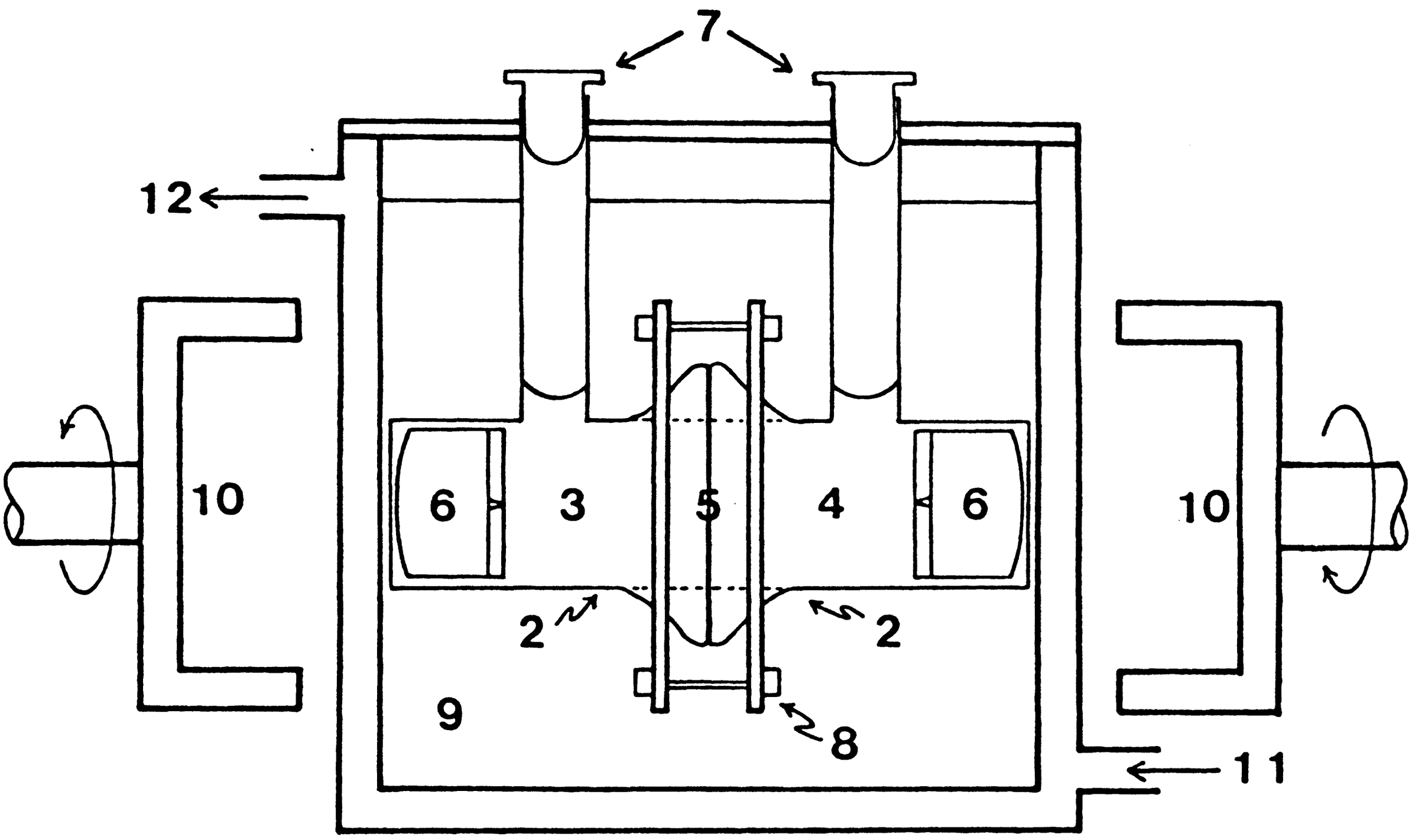

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Figure 6. Illustration of the diffusion cell type 2 used in the permeation experiments.

1. jacketed container; 2, glass cell; 3, donor solution; 4, receptor solution; 5, membrane; 6, magnetic spin-fin; 7, cap; 8, cell clamp; 9, bathing water; 10, magnet; 11, inlet water; 12, outlet water.

Stirring condition is reported to contribute much to the release rate of drug in relation to diffusion layer effect[55]. A preliminary experiment showed that a rotating speed of less than 200 rpm resulted in significantly slow release of the drug, and that increasing the speed more than 400 rpm did not give any noticeable increase in release rate. In this experiment, the rotating speed was kept at around 500 rpm. Ten milliliters of solution occupied each compartment. A hydrochloric acid solution at pH 1.0 was placed in the receptor compartment. At scheduled times, an aliquot of the receptor solution was pipetted out for UV determination and the same volume of the hydrochloric acid solution was added to the receptor compartment to replace the reduced volume. After dilution of the sample with pH 6 phosphate buffer, UV absorbance of the unprotonated drug was measured at 287 nm.

Permeation Experiments Using Diffusion Cell Type 3 --- Diffusion cell type 3 is illustrated schematically in Fig. 7. The composition of this cell is essentially the same as that of type 2. The volumes of donor and receptor compartments were 45 ml and 72 ml, respectively. The membrane area available for diffusion was 12.6 cm^2. The rotating speed of spin-fin (35 mm in diameter and 12 mm in thickness) was kept at around 400 rpm. At scheduled times, 25 ml of the receptor solution was pipetted out for UV determination and the same volume of the hydrochloric acid solution was added. UV absorbance of the protonated drug was read at λ_{max} of each drug in acidic solutions at pH 1.0: 227 nm for butamben, n-pentyl p-aminobenzoate, and procaine; 229 nm for

tetracaine; and 263 nm for lidocaine.

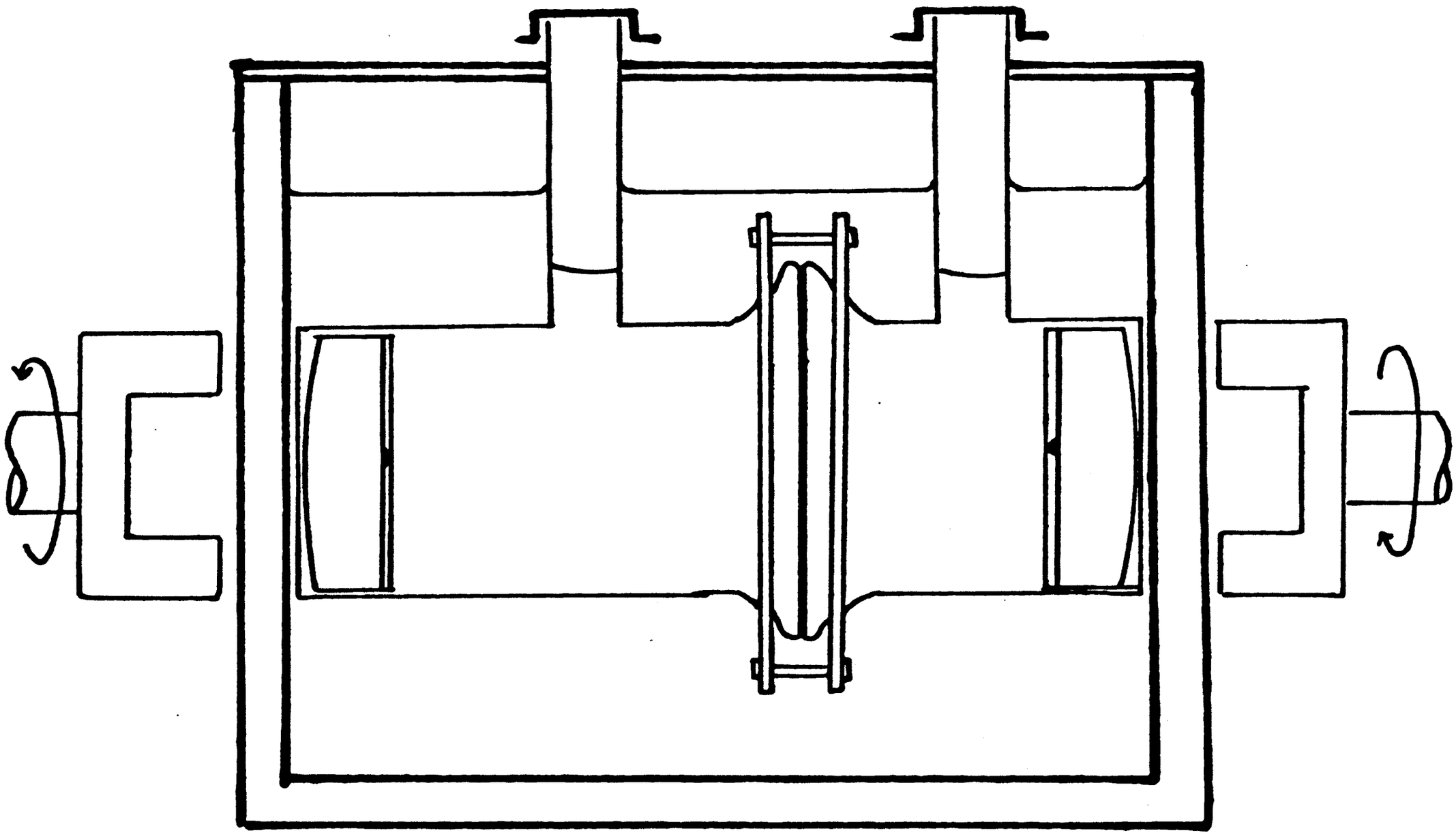


Figure 7. Illustration of the diffusion cell type 3 used in the permeation experiments.

Each part corresponds to that of the cell type 2.

3-4 Permeation Experiments Using Capsules

Preparation of Silicone Capsules --- Two types of capsules were prepared from Silastic medical grade tubings. Capsule type 1, prepared from tubing 6.4 mm inner diameter and 9.5 mm outer diameter, had an inner volume of 1 ml; whereas capsule type 2, prepared from tubing 3.35 mm i.d. and 4.65 mm o.d., had an inner volume of 0.2 ml. The tubes were cut into cylinders of the appropriate length. In capsule type 1, both ends were closed by polymethyl methacrylate plates (3-mm thick, one of which had a hole in the center) cemented in place with Silastic Medical Adhesive Type A. After allowing the adhesive to harden for 20 hours, 1 ml of a test solution was introduced into the capsule with a syringe through the hole. The opening was then sealed with the adhesive. In capsule type 2, both ends were closed by glass beads (3.5-mm diameter) with the adhesive.

Permeation Experiments --- The release rate of butamben from the capsules in vitro was measured at 37.0 ± 0.5°. Capsules were suspended with a cotton thread in erlenmeyer flasks or test tubes containing hydrochloric acid solutions at pH 1.0. The flasks or tubes were immersed in a constant temperature bath. At given intervals, capsules were taken out, quickly rinsed with distilled water, wiped free of water to prevent possible carry-over, and transferred to vessels containing fresh hydrochloric acid solutions at 37°. A fresh hydrochloric acid solution was employed as the desorbing medium at each sampling time in order to maintain a sink condition. UV absorbance of the desorbing solution was read at 227 nm, the λ_{max} of protonated

butamben in the hydrochloric acid solution. The amount of the drug release was calculated from the absorbance data. Most of the release rate experiments in vitro were carried out in triplicate.

4. Release Studies In Vivo

The same silicone capsules as those used in the studies in vitro (capsule type 1) were implanted subcutaneously in the dorsal side of rabbits anesthetized by means of a sodium pentobarbital injection. The amount of drug released from the capsules was measured every other day up to 10 days. At scheduled time, the capsule was removed from the implanted site and rinsed with distilled water. After cutting the capsule open with a blade, 0.5 ml of the contents was pipetted out and diluted appropriately with distilled water. UV absorbance of the diluted sample was read at 287 nm, the λ_{max} of unionized butamben in water. The amount of drug released was calculated by subtracting the amount remaining in the capsule from that introduced initially. No substance which might penetrate into the capsule and interfere with the UV assay was detected. The release studies in vivo were carried out in triplicate.

5. Source of Materials Used

Butamben (n-butyl p-aminobenzoate), benzocaine (ethyl p-aminobenzoate), p-nitrobenzoyl chloride, n-pentyl alcohol, and 7-(2-hydroxyethyl)theophylline, all of reagent grade, dodecyltrimethylammonium chloride, and sodium alginate were purchased from Tokyo Kasei Kogyo Co., Tokyo; methyl cellulose-500 cps and 4000 cps, caffeine monohydrate, reagent grade, polysorbate 80, sodium dodecyl sulfate, laurylpyridinium chloride, macrogol (polyethylene glycol) 400 and 20000, from Wako Pure Chemical Industries, Osaka; polyoxyethylene lauryl ether (BL-9EX), from Nikko Chemicals, Tokyo; povidone K-15 (average MW ≃ 10000), from Daiichi Pure Chemicals, Tokyo; α-cyclodextrin, from Teijin Co., Tokyo; cotton seed oil, from Hayashi Ichiji Shohten, Tokyo; procaine hydrochloride, JP grade, from Iwaki Pharmaceuticals, Tokyo; tetracaine hydrochloride, from Kyorin Pharmaceuticals, Tokyo; and lidocaine, from Fujisawa Pharmaceutical Industries, Osaka.

n- Pentyl p-aminobenzoate was synthetized following the procedures described by E. Epstein et al.[56] starting from p-nitrobenzoyl chloride and n-pentyl alcohol. The final product was identified as n-pentyl p-aminobenzoate by the following analytical data:

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76;
Found: C, 69.54; H, 8.51; N, 6.82.

$UV\lambda_{max}^{H_2O}$ nm(ε): 285(17500), $UV\lambda_{max}^{HCl(pH1.0)}$ nm(ε): 227(12850).

Silicone membranes (Silastic medical grade silicone rubber sheeting, nonreinforced) in labeled thicknesses of 0.005 and 0.01 inches, silicone tubings (Silastic medical grade tubing) 6.4 mm

inner diameter and 9.5 mm outer diameter and 3.35 mm i.d. and 4.65 mm o.d., and Silastic Medical Adhesive Type A were purchased from Dow Corning, Midland, Michigan. Ethylene-vinyl acetate membrane (EVAFLEX, vinyl acetate content of 17%, labeled thickness of 0.018 mm) was obtained from Mitsui Polychemicals Co., Tokyo.

All chemicals were used as received. Silicone membranes and tubings were washed with distilled water and ethanol before use.

6. Instrumentations

A double-beam/difference/dual-wavelength recording spectrophotometer (Model UV-300, Shimadzu Manufacturing Co., Tokyo) was used in the hydrolysis studies. A dual-wavelength spectrophotometer (Model 556, Hitachi Manufacturing Co., Tokyo) was used in the solubility study in the presence of UV-absorbing interfering substances. In other spectrophotometrical assays, Hitachi double-beam spectrophotometer, Model 200-20, was used.

A gas-liquid chromatograph (Shimadzu Model GC-4APF) was used in the solubility study.

An incubator (Model M-100^{T}, Taiyo Kagaku Kogyo Co., Tokyo) was used as a constant temperature shaking bath. A constant temperature bath (Model FS, Haake, Berlin) and DC motors equipped with rotating-speed meters (Model DC-6R, Tokyo Rikakikai, Tokyo) were employed in the permeation experiments using diffusion cells type 2 and 3.

In preparation of emulsions, an ultrasonic vibrator (Model UR-200P, Tomy Seiko Co., Tokyo) was used.

PART I: STUDIES ON THE SELECTION OF A SUITABLE DRUG

1. Some Physicochemical Properties of Several Local Anesthetics and Their Permeabilities to the Silicone Membrane[57)]

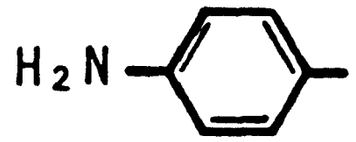
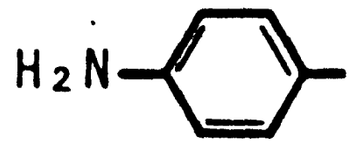
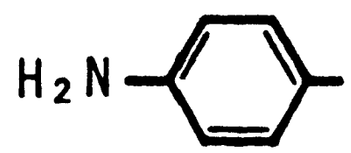
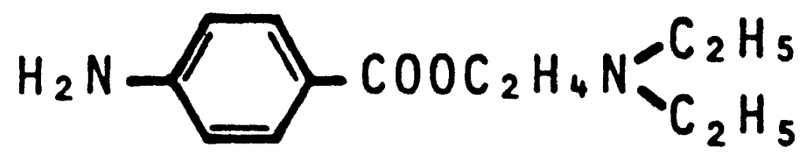
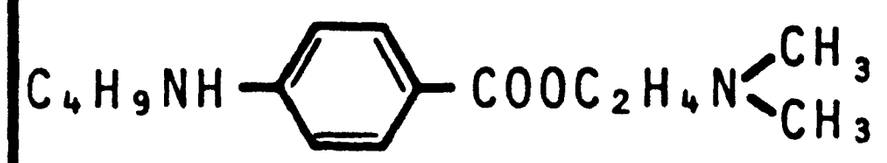
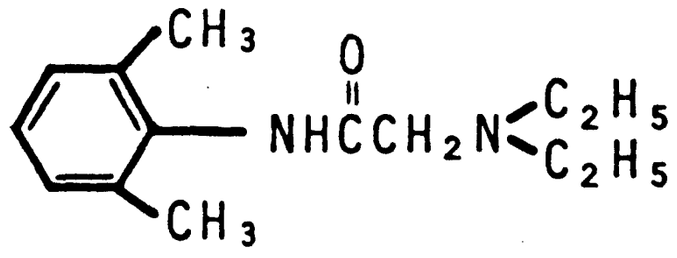
In Table 1 are listed the local anesthetics examined along with pKa values and permeabilities to silicone membrane. Generally, useful local anesthetics contain a lipophilic (mostly aromatic) portion, an intermediate chain, and a hydrophilic (often substituted tertiary amino) group in their chemical structures. Such structural characteristics can be seen in those drugs listed here (procaine, tetracaine, and lidocaine). Most local anesthetics have their pKa's between 8 and 9 on the tertiary amino group, below which positively charged (less lipophilic) molecules are dominant in solutions.

On the other hand, benzocaine, butamben, and n-pentyl p-aminobenzoate, because of the absence of tertiary amino group, have very low pKa values above which uncharged forms are dominant in solutions.

In the last column, permeability of each local anesthetic to the silicone membrane is shown. The order in magnitude of P (procaine $<$ lidocaine $<$ tetracaine) is in good agreement with that of lipophilicity as well as the local anesthetic potency[58-60)]. Compared to those drugs, benzocaine, butamben, and the n-pentyl ester showed rather high permeabilities so that these drugs are also expected to be potent. In fact, benzocaine is reported to be a potent local anesthetic[61)].

In order to release a drug having pKa above through such a membrane as silicone, pH of a drug solution must be above 9

Table I. pKa Values and Permeabilities to Silicone Membrane of Local Anesthetics Examined

Formula	Names	pKa values*	P at 30°, cm^2/sec** (donor medium, pH)
	Ethyl p-aminobenzoate (Benzocaine)	2.54	1.3×10^{-6}*** (H_2O, pH 5.5)
	n-Butyl p-aminobenzoate (Butamben)	≈ 2.5	1.2×10^{-5} (H_2O, pH 5.5)
	n-Pentyl p-aminobenzoate	≈ 2.5	1.9×10^{-5} (H_2O, pH 5.5)
	Procaine	9.02	9.9×10^{-8} (Buffer, pH 11)
	Tetracaine	8.48	6.5×10^{-6} (Buffer, pH 11)
	Lidocaine	7.97	2.7×10^{-6} (Buffer, pH 10)

* in H_2O, μ =0.1 (KCl), at 20°, from Ref. 62.

** determined by permeation studies using diffusion cell type 3, 0.005-inch Silastic membrane.

*** determined by permeation study using diffusion cell type 2, 0.01-inch Silastic membrane.

to keep the drug in an uncharged (permeable) form.

Alkalinization of the medium, on the other hand, may cause hydrolytic breakdown of a local anesthetic, especially of an ester type (procaine, tetracaine)[63-65]. As benzocaine, butamben, and the n-pentyl ester have low pKa values, their releases from solutions of neutral pH range through a silicone membrane is attainable. From a standpoint of chemical stability, the use of a neutral pH condition is preferable.

For the series of n-alkyl p-aminobenzoates, the permeability to a silicone membrane, which is closely related to lipophilicity, increases with an increase in the length of a side alkyl chain as water solubility decreases[55]. A similar result was obtained in the present study (Table 1).

In Fig. 8 are shown the release profiles of benzocaine and butamben through a silicone membrane from aqueous suspensions using diffusion cell type 1. Both drugs were released at nearly the same rate. The release rate of drug from its suspension is a function of permeability and solubility as well as a membrane thickness (Eq. 7). As a result, parabolical relationship between the flux and side-chain length exists. The maximum steady-state flux through a silicone membrane was reported to be obtained when a saturated solution of n-propyl or n-butyl ester was applied[55].

Similar release experiments were carried out by using diffusion cell type 2 and the result is shown in Fig. 9. Butamben was released at a higher rate than benzocaine. This result is in agreement with the reported one. Aqueous solubilities of benzocaine, butamben, and the n-pentyl ester were determined

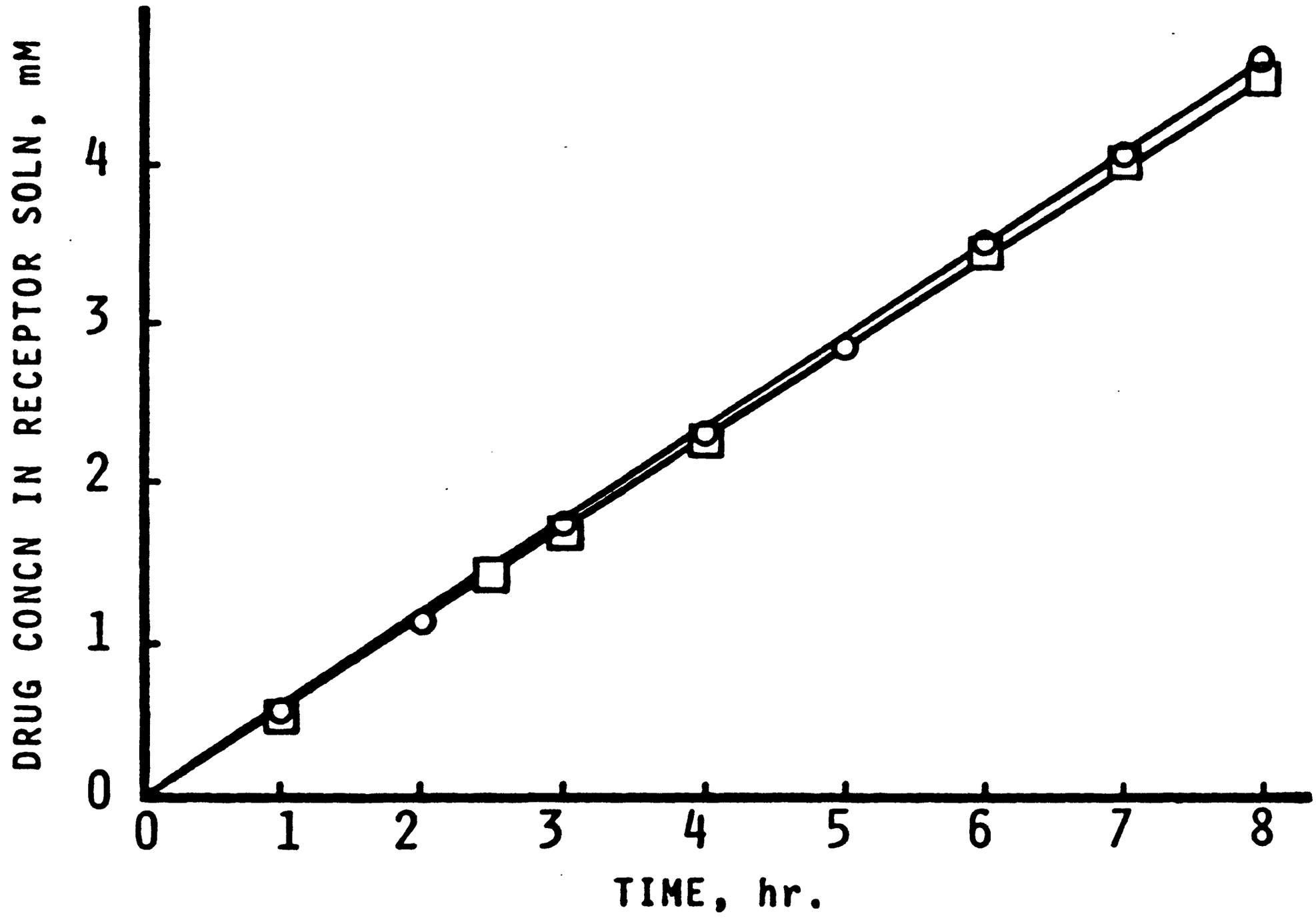


Figure 8. Release profiles of benzocaine (○) and butamben (□) through the silicone membrane (0.005 inch thick) from their suspensions in water stirred by propellers at 30°. Diffusion cell type 1 was used.

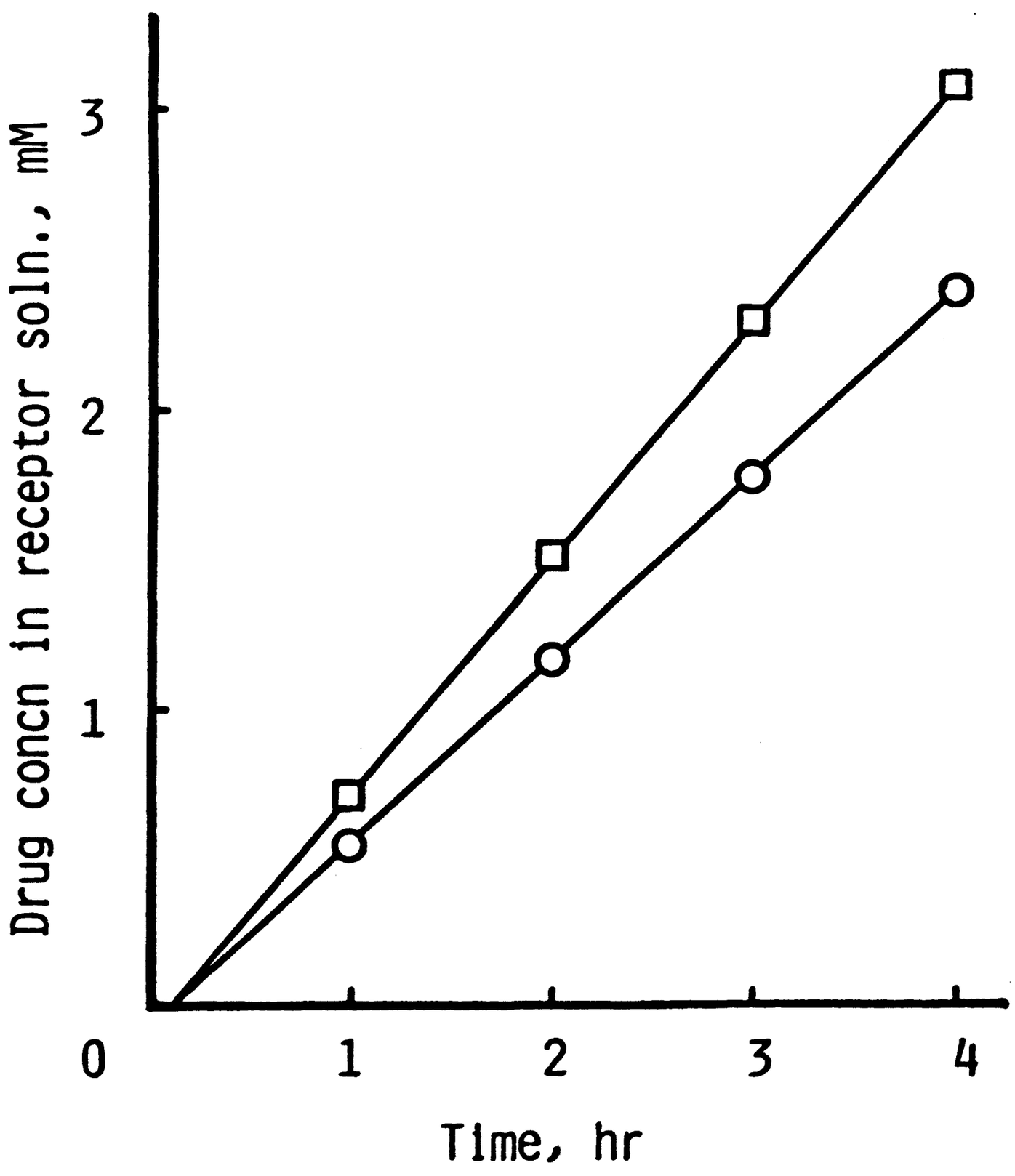


Figure 9. Release profiles of benzocaine (O) and butamben (□) through the silicone membrane (0.01 inch thick) from their suspensions in water at 30°. Diffusion cell type 2 was used.

at 30° to be 7.5, 1.2, and 0.27 mM, respectively. The product of solubility and permeability (listed in Table 1) can be calculated: 0.975×10^{-11}, 1.44×10^{-11}, 0.513×10^{-11} moles/cm/sec for benzocaine, butamben, and the n-pentyl ester, respectively. From these results, among the three drugs, butamben proved to give the highest flux through a silicone membrane from a saturated solution. The reduced release rate of butamben in Fig. 8, even though the contents in both compartments were stirred by motor-driven propellers, can be attributed to insufficient dispersion of drug particles in the donor solution. Possible dissolution rate-limited release of drug in a suspension system with considerably low water solubility was also indicated.

2. Comparison of Benzocaine and Butamben for Their Stabilities to Hydrolysis[57)]

From those results in the previous section, it is suggested that n-alkyl p-aminobenzoate esters are useful agents for silicone membrane-controlled release on the basis of their permeabilities and chemical stabilities.

As stated in the previous section, these drugs can be introduced to the system in solutions of a neutral range. Under such conditions, these drugs are rather chemically stable. If kept on standing for an extended period of time, they should undergo hydrolytic breakdown to some extent.

In order to consider further on selecting a suitable agent for the delivery system among the homologs, stabilities of benzocaine and butamben to hydrolytic breakdown were compared.

As shown in Fig. 10, semi-logarithmic plots of the concentra-

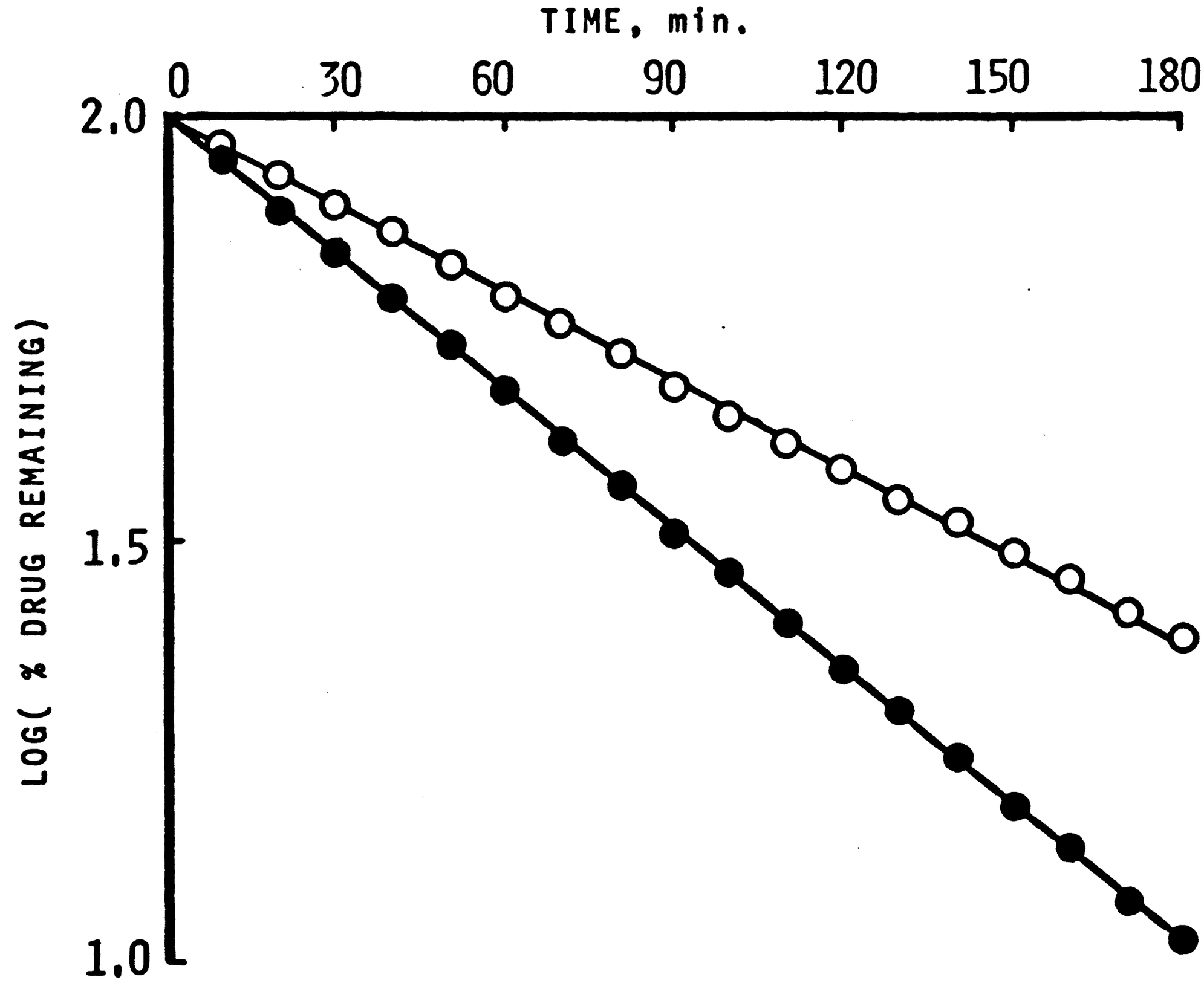


Figure 10. Rates of hydrolysis of benzocaine (●) and butamben (○) in 0.05N NaOH solutions at 30°.

tions of unhydrolyzed benzocaine and butamben vs. time gave linear profiles (pseudo-first-order reaction). The rate constant k and the half-life for the reaction were determined from the slope and are listed in Table II. Benzocaine was found to be hydrolyzed more rapidly than butamben, indicating that butamben is more stable against hydrolysis in alkaline solutions than benzocaine. A similar observation has been reported recently by Smith, et al.[66)]

In suspensions, the concentration of the drug in solution is kept constant at its solubility, Cs. The rate of hydrolysis -dC/dt can then be written by:

$$-\frac{dC}{dt} = kCs$$

where k = first-order rate constant. Since both k and Cs are constant at constant temperature and pH, the rate of hydrolysis becomes constant (zero-order reaction). First-order rate constants, solubilities, and rates in suspensions for benzocaine and butamben are listed in Table II. It can be interpreted that butamben in suspension is more stable against alkaline hydrolysis than benzocaine in suspension by about 10 folds due to its lower solubility and smaller rate constant against hydrolysis.

Table II. Solubilities and Rate Constants of Hydrolysis at 30°

Anesthetics	Solubility Cs, mM	Rate constant 10^3k, min^{-1}	Half-life of hydrolysis, min^{-1}	10^6k Cs M min^{-1}
Benzocaine	7.5	12.5	55.4	93.8
Butamben	1.2	7.97	86.9	9.56

3. Summary

Six local anesthetics; procaine, tetracaine, lidocaine, benzocaine, butamben, and n-pentyl p-aminobenzoate were evaluated for their possible use in a silicone membrane-controlled release system. For procaine, tetracaine, and lidocaine, alkaline conditions were needed to obtain an observable amount of release. Such conditions are not preferable from a standpoint of chemical stability. Benzocaine, butamben, and the n-pentyl ester, on the other hand, do not necessitate alkaline conditions due to their low pKa values. In addition, these n-alkyl p-aminobenzoate esters exhibit relatively high permeabilities to a silicone membrane. Among the homologs, butamben showed the highest release rate from its saturated solution.

Benzocaine and butamben were compared for their stabilities against hydrolytic degradations in 0.05N NaOH solutions. Calculated stability of butamben in suspensions was about 10 times greater than benzocaine due to a smaller hydrolytic rate constant and smaller solubility.

From those studies on permeability and stability, it may be suggested that butamben is preferable to the other local anesthetics examined herein when used in the delivery system employing a partition membrane as a release-controlling barrier. It can be generally stated that in such a delivery system, examinations of a drug for its permeability to the membrane and stability in the reservoir give a meaningful suggestion to a proper choice of a drug from a series of homologs.

PART II: RELEASE OF BUTAMBEN FROM SYSTEMS CONTAINING SOLUBLE COMPLEXES

1. Solubilization of Butamben by Complex Formation[24,30)]

In Fig. 11, the solubilities of butamben in solutions of five complexing agents are presented. The solubility of the drug increased linearly with the concentration of povidone, 7-(2-hydroxyethyl)theophylline (HET), caffeine, and α-cyclodextrin. The linearity was observed only in the concentration range up to 1.1% for β-cyclodextrin, indicating that β-cyclodextrin formed a complex with a limited solubility (the solubility of the complex was calculated to be 7 mM at 30°).

With the assumption that these complexes are of the 1:1 type, stability constants of butamben complexes were calculated by the Higuchi and Connors equation[31)] to be $5.4 \times 10^2 M^{-1}$, $2.2 \times 10^3\ M^{-1}$, $61\ M^{-1}$, $32\ M^{-1}$, and $2.9\ M^{-1}$ for α-cyclodextrin, β-cyclodextrin, HET, and povidone (where the molecular weight of the repeating unit, vinylpyrrolidone, was used in the calculation), respectively. Thus, cyclodextrins, especially β-cyclodextrin, were found to form stable complexes with butamben. Then follows caffeine, and HET, which is less hydrophobic than caffeine, interacted rather weakly with butamben. The interaction between povidone and butamben was very small.

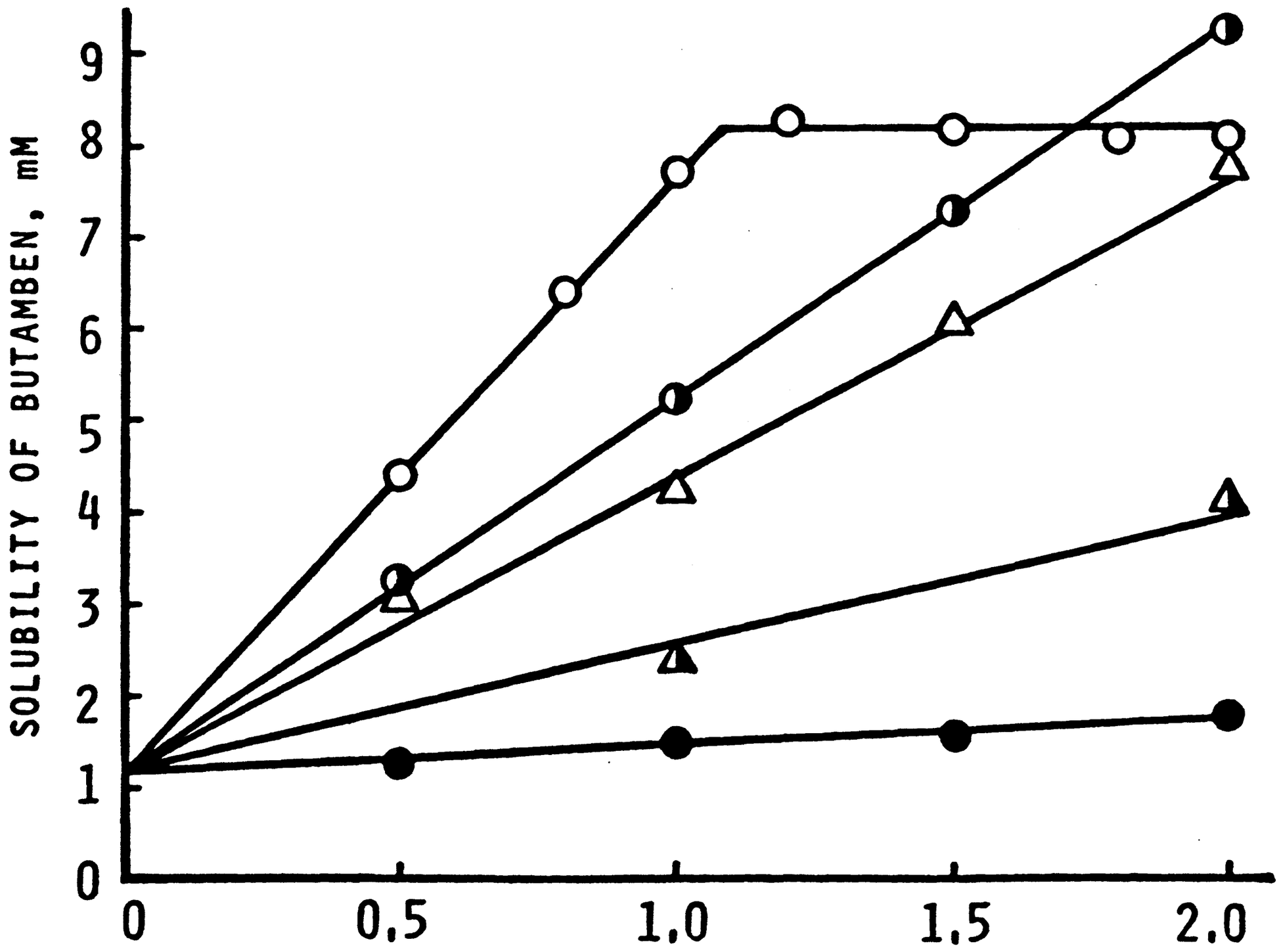


Figure 11. Solubility profiles of butamben in solutions of ◑, α-cyclodextrin; ○, β-cyclodextrin; △, caffeine; ▲, 7-(2-hydroxyethyl)theophylline; and ●, povidone at 30°.

2. Release Profiles of Butamben from Systems Containing Soluble Complexes[24,30)]

Permeation profiles of the drug from suspension systems, which may give a maximum release rate, can be a good reference to evaluate each system containing a complexing agent. Before the effects of complexation on permeation are considered, permeation of butamben from suspensions were examined.

In Fig. 12 are shown the permeation behaviors of butamben from the suspensions in water, 0.1% and 0.25% methylcellulose solutions. Although the solubilities of butamben were the same in the three cases, the permeation profiles varied significantly. When the concentration of methylcellulose was increased from 0.1% to 0.25%, the release rate slowed down and a constant (zero-order) release was no longer obtained in spite of increased drug-suspending action. The release rate of butamben was greater from the propeller-stirred suspension in water than from the two methylcellulose suspensions, indicating that the better dispersion and reduced diffusion layer thickness around the solid in the former favor the dissolution of the drug which, in turn, favors the transport of the drug. It can then be stated that the release rate of butamben in the methylcellulose suspension systems is not membrane-limited. Such an incidence might occur for the drug with considerably slow dissolution rate.

Permeation profiles of butamben from its saturated solutions in solutions of various complexing agents, and from the plain saturated solution (no solid nor complexing agent) are shown in Fig. 13. When the plain saturated solution was used as a donor

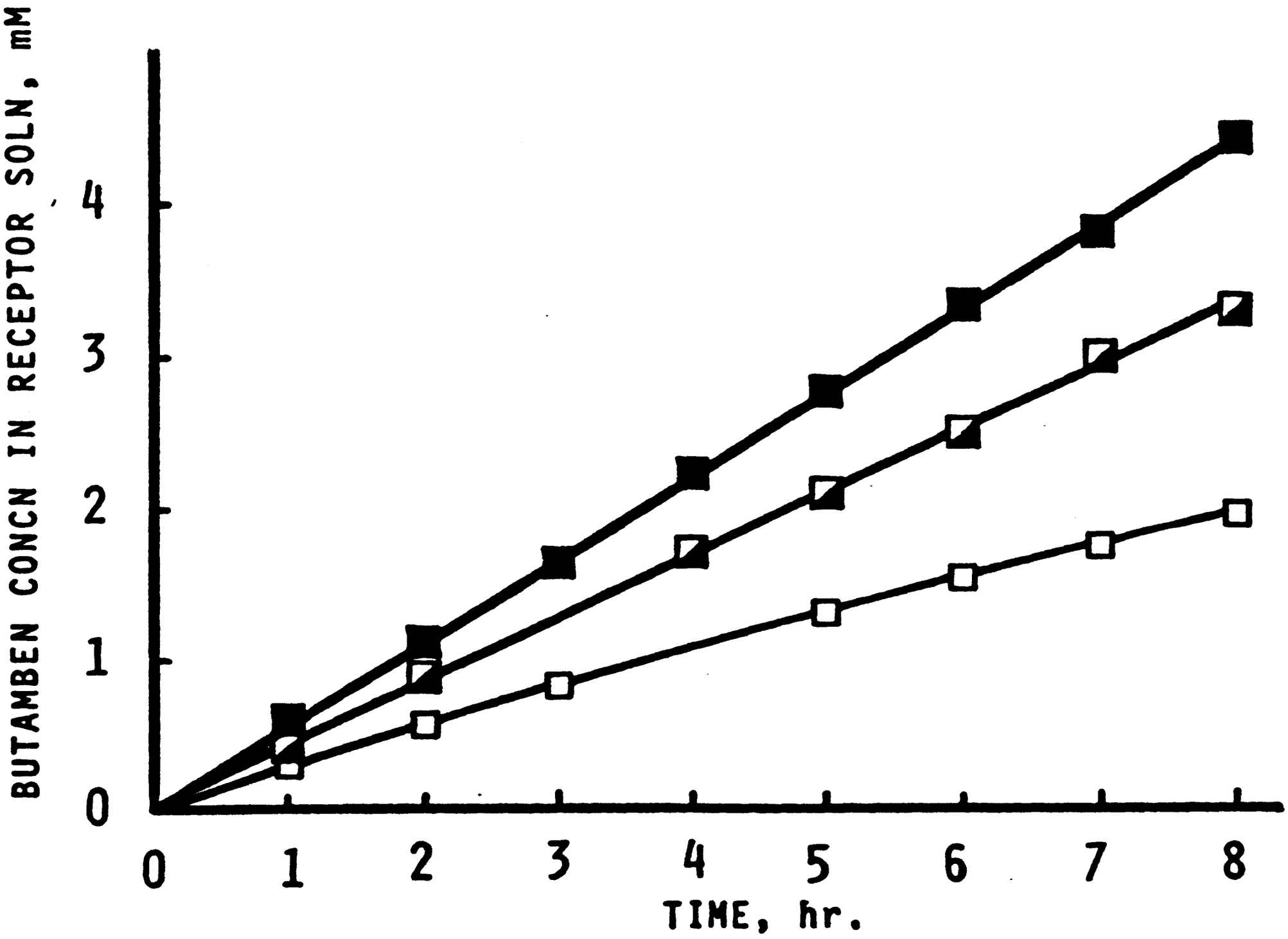


Figure 12. Release profiles of butamben through the silicone membrane (0.005 inch thick) from its suspensions in ■, water stirred by propeller; ◪, 0.1% methylcellulose; and □, 0.25% methylcellulose at 30°. Diffusion cell type 1 was used.

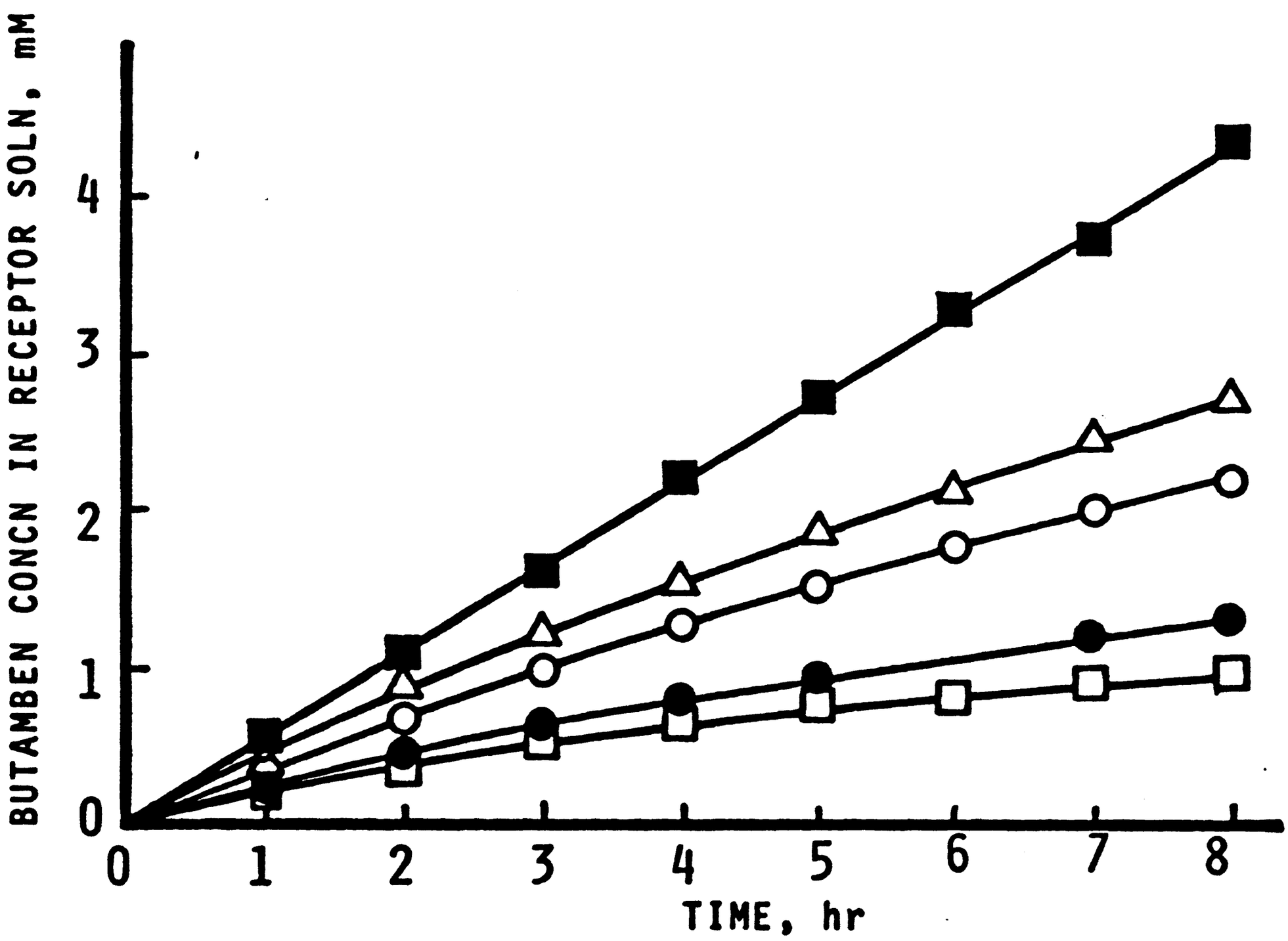


Figure 13. Release profiles of butamben through the silicone membrane (0.005 inch thick) from its initially saturated solutions in △, 2% caffeine; ○, 1% β-cyclodextrin; ●, 2% povidone; and □, water at 30°. ■, suspension in water stirred by propeller. Diffusion cell type 1 was used.

solution, the rate of release decreased rapidly as concentration in the donor solution decreased. Only about 20% of the drug remained in the donor solution after 8 hr. When saturated solutions of the drug containing complexing agents were used, the release curve fell between the line representing the permeation from the suspension and the curve for the plain solution, indicating that complexation has effects on the permeation pattern of the drug.

Before further considerations, it is necessary to discuss the possibility of permeation of species other than the free (uncomplexed) drug, such as the complexing agents or the complexes, although this possibility was assumed not to be the case in the section of THEORETICAL CONSIDERATIONS. Among the complexing agents employed in this section, α and β-cyclodextrins and povidone are assumed not to permeate through the membrane to a detectable extent due to their negligible lipophilicity. Caffeine and 7-(2-hydroxyethyl)theophylline (HET), on the other hand, do permeate through the membrane. However, much smaller permeabilities of caffeine ($P = 8 \times 10^{-9} cm^2/sec$)[32] and HET* in comparison with that of butamben ($P = 1.2 \times 10^{-5} cm^2/sec$) warrant the assumption that the concentration of caffeine or HET in the donor solution remains essentially constant throughout the permeation study.

As for the permeation of the complexed species, the cyclodextrins and povidone complexes may be considered impermeable

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*Preliminary experiments showed that less than 0.1% of the total drug permeated in 7 days.

since these complexing agents do not partition into the silicone membrane. If the caffeine and HET complexes had permeated at a significant rate, the initial release rate of butamben from these systems would have been much greater than those from the drug suspension, since several times as much drug is present in these systems as in the plain saturated solution. This, however, was not the case. The permeability of the caffeine-butamben complex or HET-butamben complex, if any, is expected to be much smaller than that of free butamben. Thus, the permeable species in the systems examined here is assumed to be essentially the free (uncomplexed) drug alone.

Fig. 11 (in the solubility studies) provides information concerning the exact amount of the free and complexed drug present in the donor solution of the three systems (caffeine, HET, and povidone) at zero time. At zero time, the amount of the free drug was the same in all systems. The drug solubilized by each complexing agent is given by the corresponding y-axis values minus the solubility of the drug in plain water.

In the povidone system, the amount of the drug solubilized was small. The cumulative amount of the drug permeated in the 8-hr period, although larger than that from the plain saturated solution, was much smaller than in the other two systems.

In 2% caffeine and 1% β-cyclodextrin systems, the solubilities of butamben were the same (7.7 mM, in Fig. 11). Therefore, the total amounts of drug (free and complexed) for permeation were the same even with different stability constant. Consequently, if the permeation studies (Fig. 13) were continued to infinite

time, the permeation profiles for these two systems would have converged to a common plateau.

Under these circumstances, since β-cyclodextrin forms a complex with a greater stability constant, the concentration of the free drug (permeable species) in the β-cyclodextrin system during the initial stage of permeation tends to be smaller than that in the caffeine system and, consequently, the release rate is initially smaller. The permeation profiles presented in Fig. 13 for the first 8-hr period clearly indicate that the rate of release was initially smaller from the β-cyclodextrin system than from the caffeine system. Since both systems should have a common plateau, the faster initial rate of release in the 2% caffeine system leads to a rapid decline in the rate and to a shorter release time than in the 1% β-cyclodextrin system.

The permeation profile from a 1% caffeine system is also shown in Fig. 14. Since the amount of total drug in 1% β-cyclodextrin was greater than that in the 1% caffeine system (Fig. 11), more drug was expected to be released from the 1% β-cyclodextrin system than from the 1% caffeine system at infinite time, even though the release rates were identical during the first 5 hr. It was suggested from these results that the rate and the duration of drug release were a function of the stability constant of complex as well as the total amount of drug added.

In order to confirm this proposition, further long-term permeation studies were carried out for 1.6% α-cyclodextrin, 1% β-cyclodextrin, and 4% HET systems using the diffusion cell type 2 (see EXPERIMENTAL section). Solubilities of butamben in

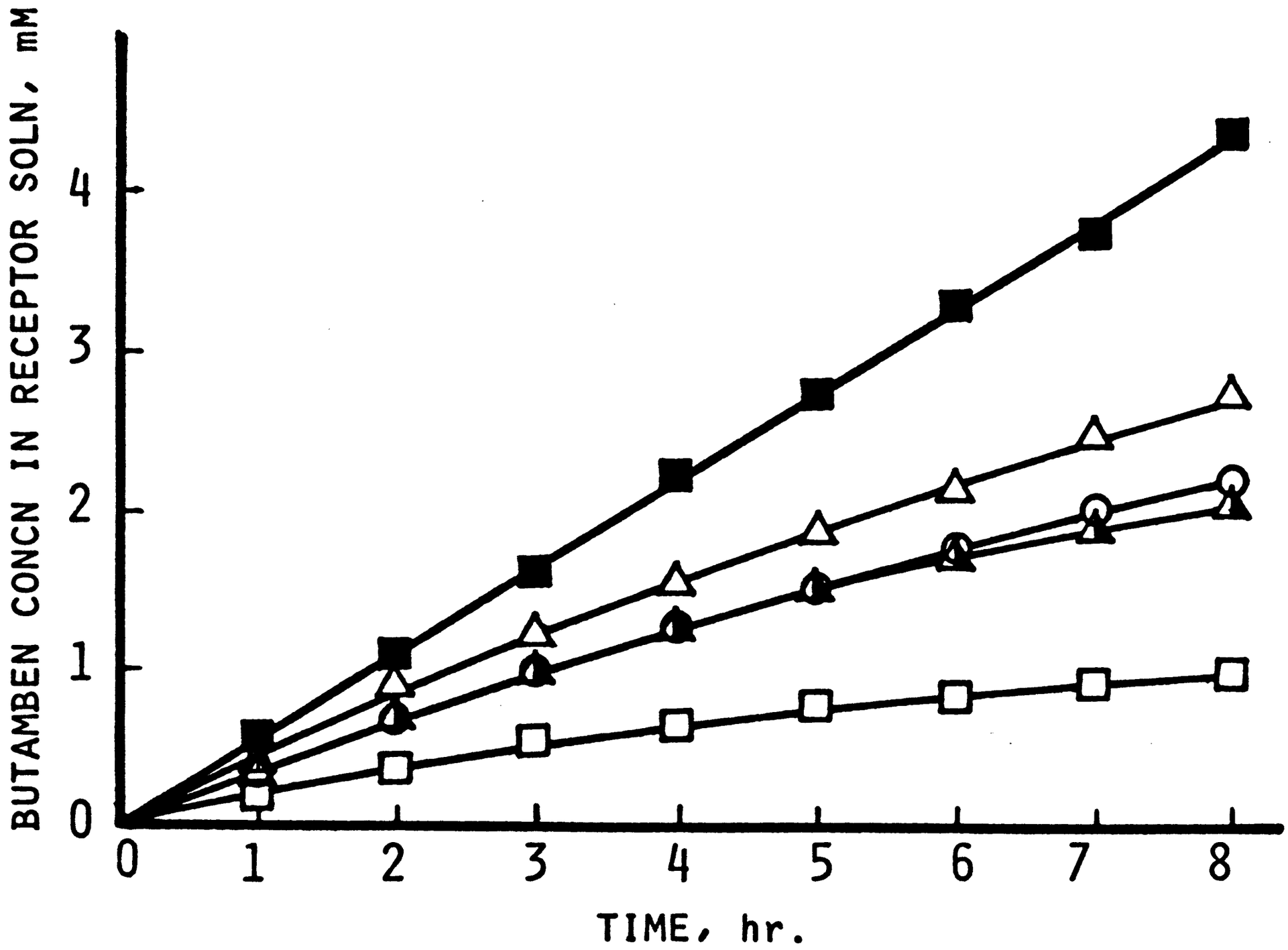

Figure 14. Release profiles of butamben through the silicone membrane (0.005 inch thick) from its initially saturated solutions in △, 2% caffeine; ▲, 1% caffeine; ○, 1% β-cyclodextrin; and □, water at 30°. ■, suspension in water stirred by propeller. Diffusion cell type 1 was used.

the three systems were all about 7.7 mM (Fig. 11). Therefore, the total amounts of the drug originally contained in the donor solutions were almost the same in the three cases, so that their permeation profiles should have a common plateau at infinite time.

The results are shown in Fig. 15. When a plain saturated solution was used, 95% of the total drug originally contained in the donor solution was released in 8 hours (Fig. 15, Inset). For the HET system, the drug was released almost completely within 60 hours. For the α- and β-cyclodextrin systems, on the other hand, the release continued even after 120 hours.

The following conclusions may therefore be drawn for the release of drug from its saturated solution containing various amounts of complexing agents. If such systems are capable of forming soluble, membrane-impermeable complexes, the release rate of drug from such systems is greater than that from the plain saturated solution of the drug, although never exceeding that from the suspension in water. Control of the release profile of drug between these limits may be possible by means of a proper choice of complexing agents. It is evident that the more stable the complex is, the greater is the reservoir of the drug available for release.

It has also been shown that for such systems as the present ones (i.e. when the saturated solution containing the same amount of drug is used), the more stable the complex is, the slower is the initial rate of release but the longer is the time required for complete release.

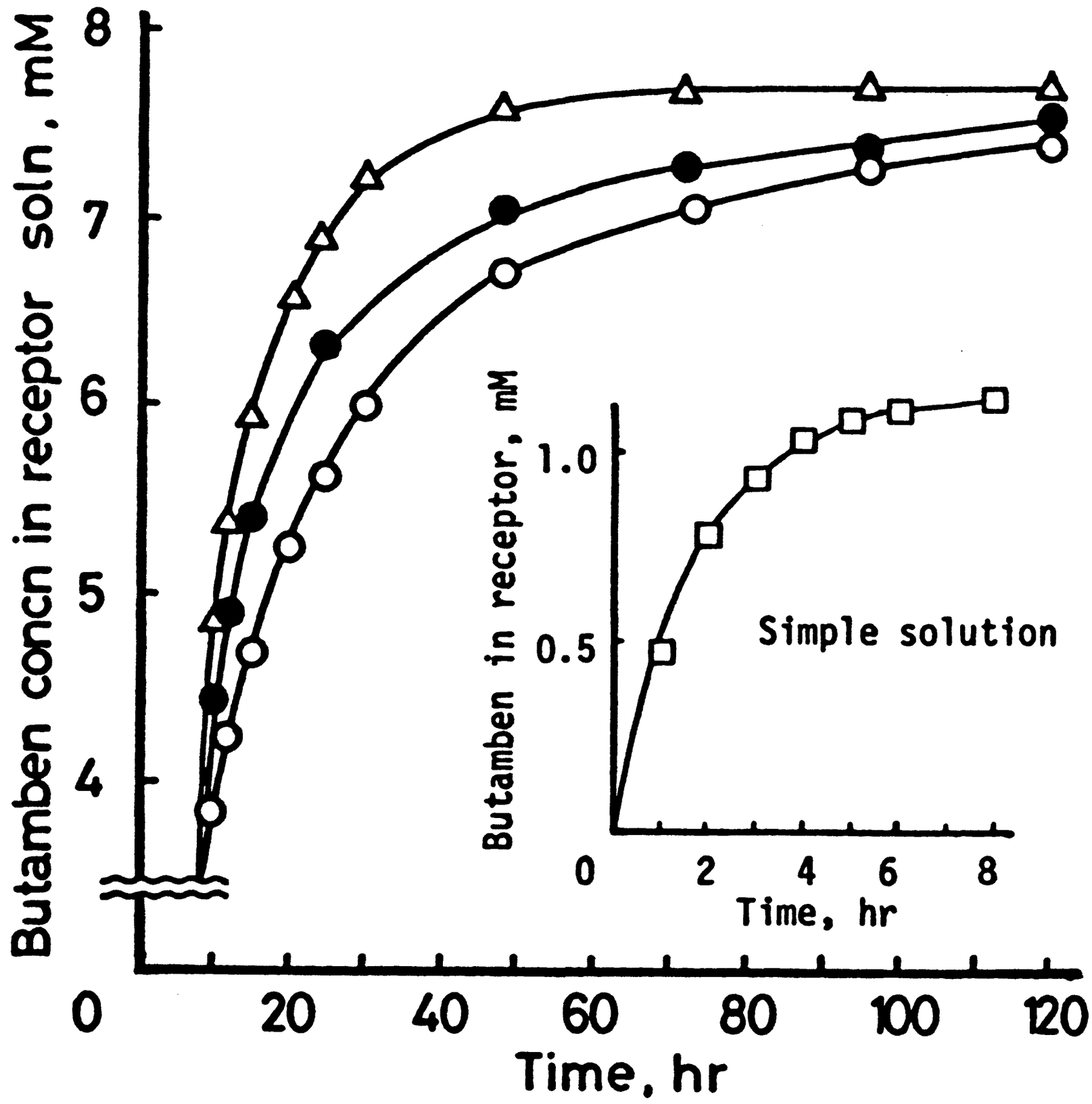

Figure 15. Long-term release profiles of butamben through the silicone membrane (0.01 inch thick) from its initially saturated solutions in ○, 1% β-cyclodextrin; ●, 1.6% α-cyclodextrin; and △, 4% 7-(2-hydroxyethyl)theophylline at 30°. Inset: □, simple saturated solution in water.

Diffusion cell type 2 was used.

3. Summary

The effects of caffeine, 7-(2-hydroxyethyl)theophylline, α-and β-cyclodextrins, and povidone on the permeation behavior of butamben from saturated solutions containing these complexing agents through a silicone membrane were investigated at 30°. Release-sustaining behavior was evaluated for the five systems. In all systems, these agents increased the rate of butamben release over the plain saturated solution. The rank order of the sustaining power was in agreement with the order of stability of each complex: the effect was more pronounced with an agent which forms a more stable complex with the drug.

From the results presented in this part, the following generalization can be made. For a fixed total (free and complexed) amount of drug available for release, sustained release is associated with systems containing more stable complexes. A desired release profile of drug can also be achieved by a proper choice of a complexing agent. Therefore, control of permeation of drug by means of complexation may find its practical value in obtaining slow sustained release from membrane-encapsulated dosage forms containing drugs in solution.

PART III: RELEASE OF BUTAMBEN FROM SYSTEMS CONTAINING MICELLES

1. Micellar Solubilization of Butamben [30]

Solubility diagrams of butamben in the presence of three types of surfactants: anionic, cationic, and nonionic surfactants, are shown in Fig. 16. The solubility of the drug increased linearly with the concentration of the surfactants above their critical micelle concentrations (cmc). Among the three surfactants used, dodecyltrimethylammonium chloride, a cationic surfactant, had a relatively high cmc (about 0.4%) and solubilized butamben to a significant extent at higher concentrations. The solubility of butamben in 2% solution of the surfactant was about 80 times that in water. Sodium dodecyl sulfate (anionic) and polysorbate 80 (nonionic) solubilized butamben similarly but to a smaller extent than dodecyltrimethylammonium chloride. Reported cmc values at 25° for the surfactants, although various values have been reported, are: around 0.2% [67-71] for sodium dodecyl sulfate; around 0.4% [72-75] for dodecyltrimethylammonium ion; and around 0.006% [76,77] for polysorbate 80. Similar values can be estimated from the diagrams shown in Fig. 16.

In contrast to butamben, benzocaine was solubilized to a smaller extent (Fig. 17). The solubility of butamben in 2% dodecyltrimethylammonium chloride solution (Fig. 16) was nearly twice that of benzocaine. Greater hydrophobicity of butamben or its higher affinity to the micelle might be a reason for a greater solubility of butamben than benzocaine. Thus, much greater amount can be retained in the surfactant solution by using butamben.

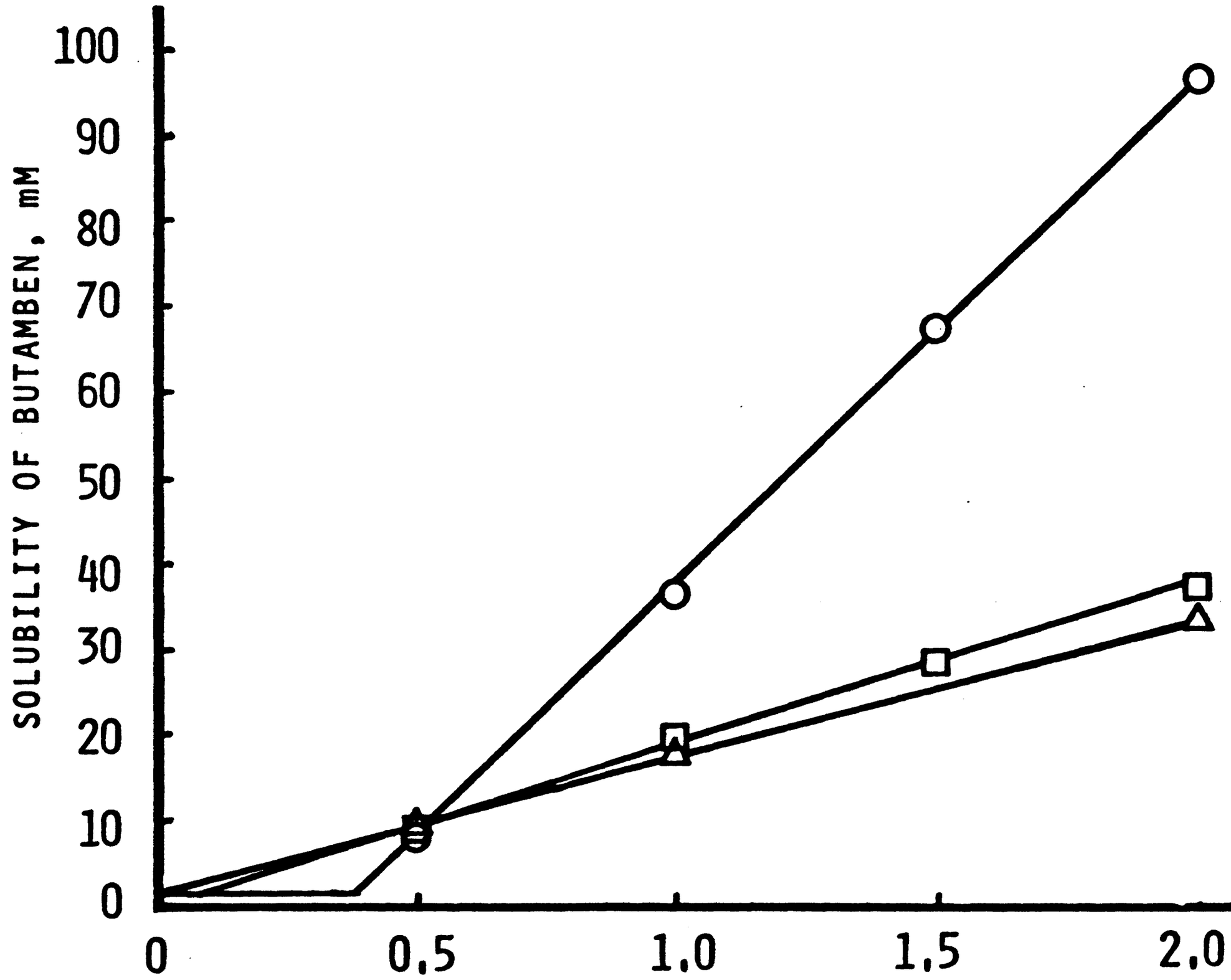

Figure 16. Solubility profiles of butamben in solutions of O, dodecyltrimethylammonium chloride; Δ, polysorbate 80; and □, sodium dodecyl sulfate at 30°.

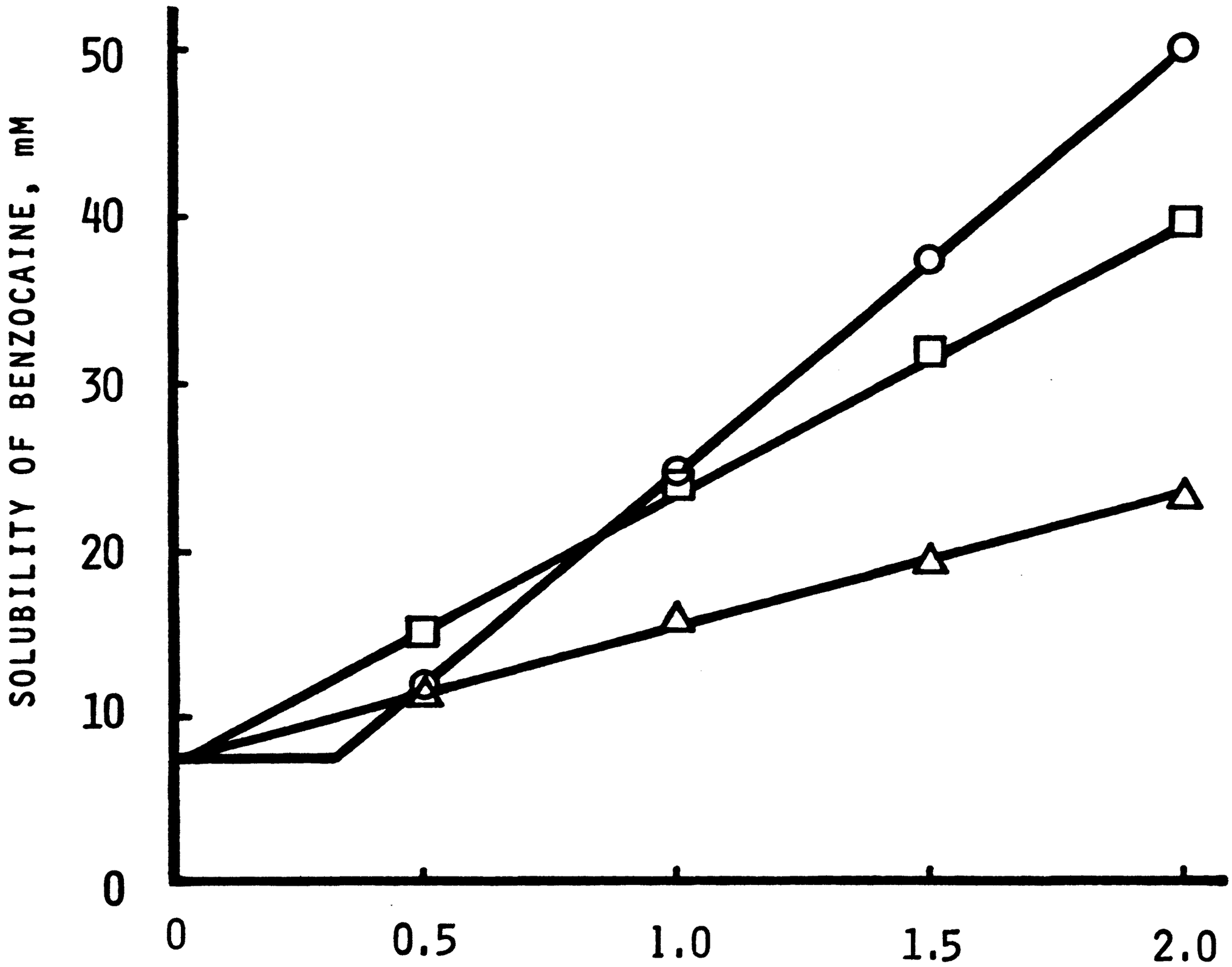

Figure 17. Solubility profiles of benzocaine in solutions of O, dodecyltrimethylammonium chloride; Δ, polysorbate 80; and □, sodium dodecyl sulfate at 30°.

2. Release Profiles of Butamben from Systems Containing Micelles

In Fig. 18 are shown short-term release profiles of butamben from its saturated solutions in 2% solutions of three surfactants: dodecyltrimethylammonium chloride, sodium dodecyl sulfate, and polysorbate 80. Up to 8 hours, a nearly constant release rate was obtained in the three cases (when the linear-regression analysis was applied to the three profiles, correlation coefficients of greater than 0.9998 were obtained). Dodecyltrimethylammonium chloride exhibited excellent ability to maintain constant release of the drug which was very close to that from the suspension. Polysorbate 80 and sodium dodecyl sulfate sustained the release to a somewhat smaller extent than dodecyltrimethylammonium chloride. The superior release-sustaining power of dodecyltrimethylammonium chloride corresponds to its greater solubilizing ability shown in Fig. 16. Therefore, a surfactant which, above its cmc, can solubilize the drug to a greater extent seems to have a larger release-sustaining power. Thus, micelles were proved to serve as reservoirs which can compensate for loss of the drug from the donor solution by partition of the drug from micelles into the bulk solution.

In Fig. 19 is illustrated a long-term release profile of butamben from its saturated solution in 2% solution of dodecyltrimethylammonium chloride. For comparison, the release profile from a butamben suspension, which was extrapolated from the short-term study up to 8 hours, is also shown. In the systems containing soluble complexes which were described in PART II, a rapid decrease in release rate was observed after 1 day. In the system

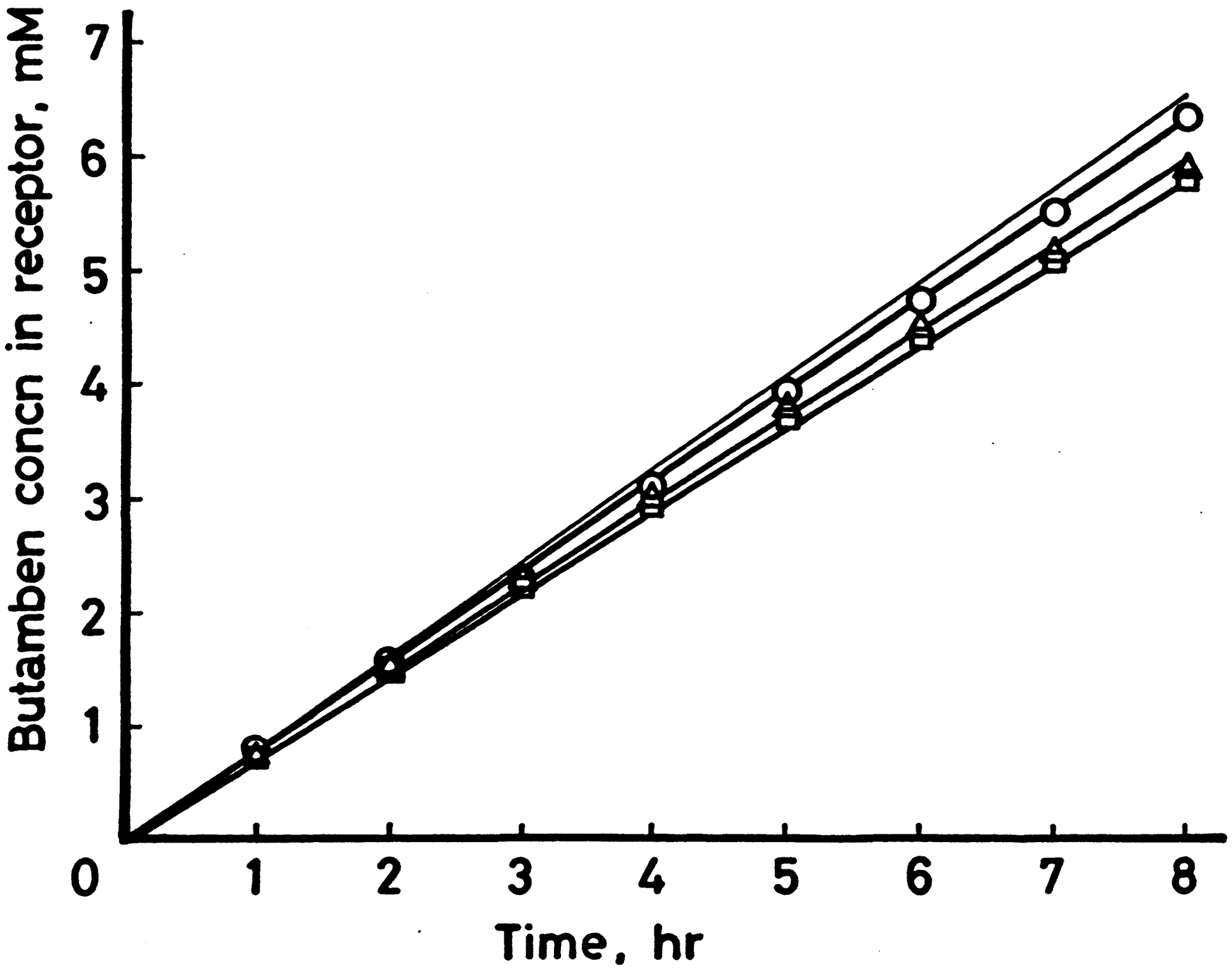

Figure 18. Release profiles of butamben through the silicone membrane (0.01 inch thick) from its initially saturated solutions in 2% solutions of O, dodecyltrimethylammonium chloride; Δ, polysorbate 80; and □, sodium dodecyl sulfate at 30°. ———, aqueous suspension. Diffusion cell type 2 was used.

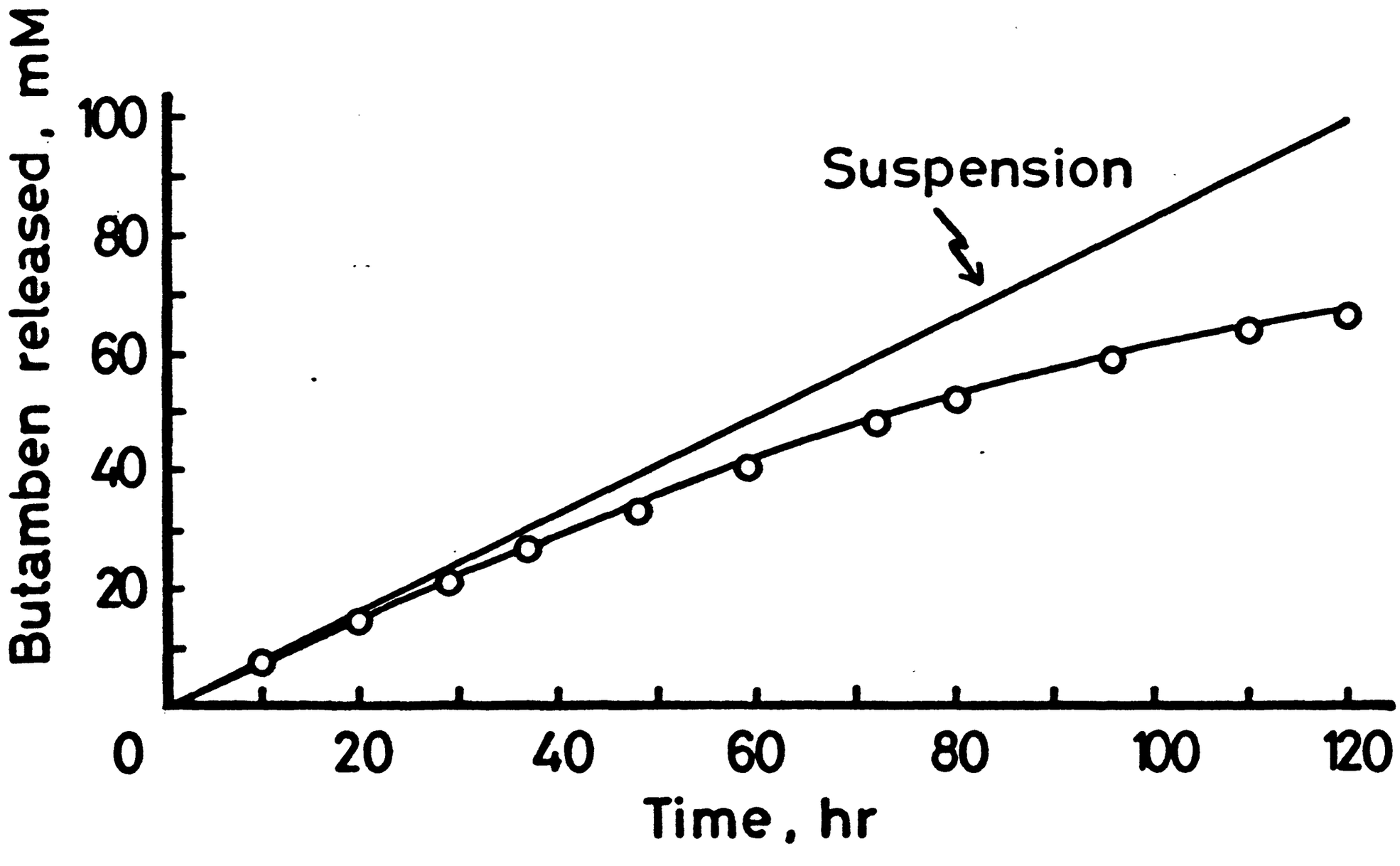

Figure 19. Long-term release profile of butamben through the silicone membrane (0.01 inch thick) from its initially saturated solution in 2% dodecyltrimethylammonium chloride solution at 30°. ———, aqueous suspension, extrapolated from the data shown in Figure 18.
Diffusion cell type 2 was used.

shown in Fig. 19, on the other hand, a decrease in release rate was very gradual although the release profile was somewhat below that from the suspension. This surfactant has proved to possess greater sustaining power in release of the drug due to its ability to retain much drug in micelles which serves as a reservoir.

3. Comparison between Theory and Experimental Results[45,46]

In the following experiments, the applicability of Eq. 15 (or its rewritten form, Eq. 16) to describe the permeation profile of drugs from the systems containing micelles has been tested.

The following terms which appear in Eq. 16 were determined directly: A = 4.52 cm^2, ℓ = 2.48 × 10^{-2} cm for silicone membrane (measured thickness whereas the labeled thickness was 0.01 inch = 2.54 × 10^{-2} cm) and 1.8 × 10^{-3} cm for ethylene-vinyl acetate copolymer membrane (labeled thickness), V = 10 ml, Cs = 1.2 × 10^{-6} moles/cm^3 (determined at 30°). Cs was determined by solubility measurements in each case. When a drug suspension is placed in the donor compartment, a constant release rate is obtained so that the P value can be calculated from Eq. 7.

It has been realized that the presence of diffusion layer should be taken into account when drug permeation through membrane is considered[55]. In fact, diffusion layer-effect have been reported for permeation of phenylbutazone through a silicone membrane[78]. In particular, the contribution of diffusion layer becomes apparent when the membrane is thin and the agitation

of solutions is mild[78]. In the present investigation, the diffusion cell type 2 was used and the solutions on both sides of the membrane were vigorously agitated (see EXPERIMENTAL section). Therefore, the assumption that contribution of the diffusion layer-effect at the membrane surface can be neglected may not cause a significant error when analyzing the data.

Fig. 20 shows release profiles of butamben from suspensions in water as well as surfactant solutions. In both cases, linear profiles are obtained during the experimental period. A slight increase in the release rate was observed in the permeation from the suspension containing a surfactant. In addition, an increase in the concentration of surfactants in the suspension showed a tendency to give a greater release rate of butamben. These observations may be attributed to the fact that the surfactant either wets the membrane surface better or promotes dissolution of the drug[79]. The P value was therefore determined in each case using a drug suspension containing a corresponding surfactant.

In Fig. 21 are shown the results for butamben in the presence of three types of surfactants. Data are presented by plotting $-\ln(1 - Mr/M_\infty)$ against time t according to Eq. 16. Data thus treated gave approximately linear profiles as were expected from the model introduced. Experimental data points fitted on theoretical lines fairly well.

Two other surfactants, anionic and cationic, were also employed to examine the applicability of the model to these systems (Fig. 22). A fit similar to that in Fig. 21 was observed. Slight deviation from theoretical lines may be attributed to

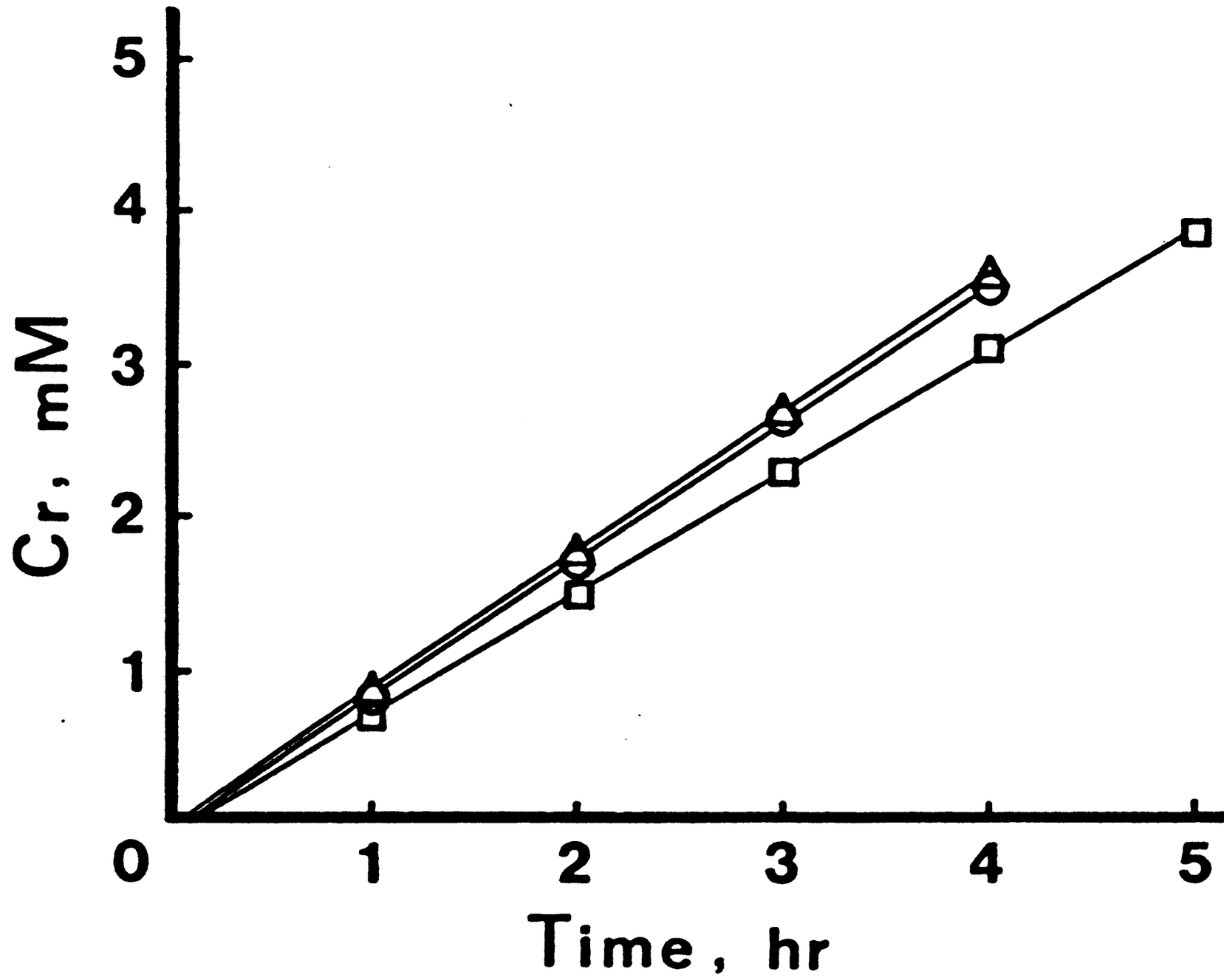

Figure 20. Release profiles of butamben through the silicone membrane (0.01 inch thick) from its suspensions in □, water; Δ, 0.5% dodecyltrimethylammonium chloride; and O, 0.5% sodium dodecyl sulfate solution at 30°. Diffusion cell type 2 was used.

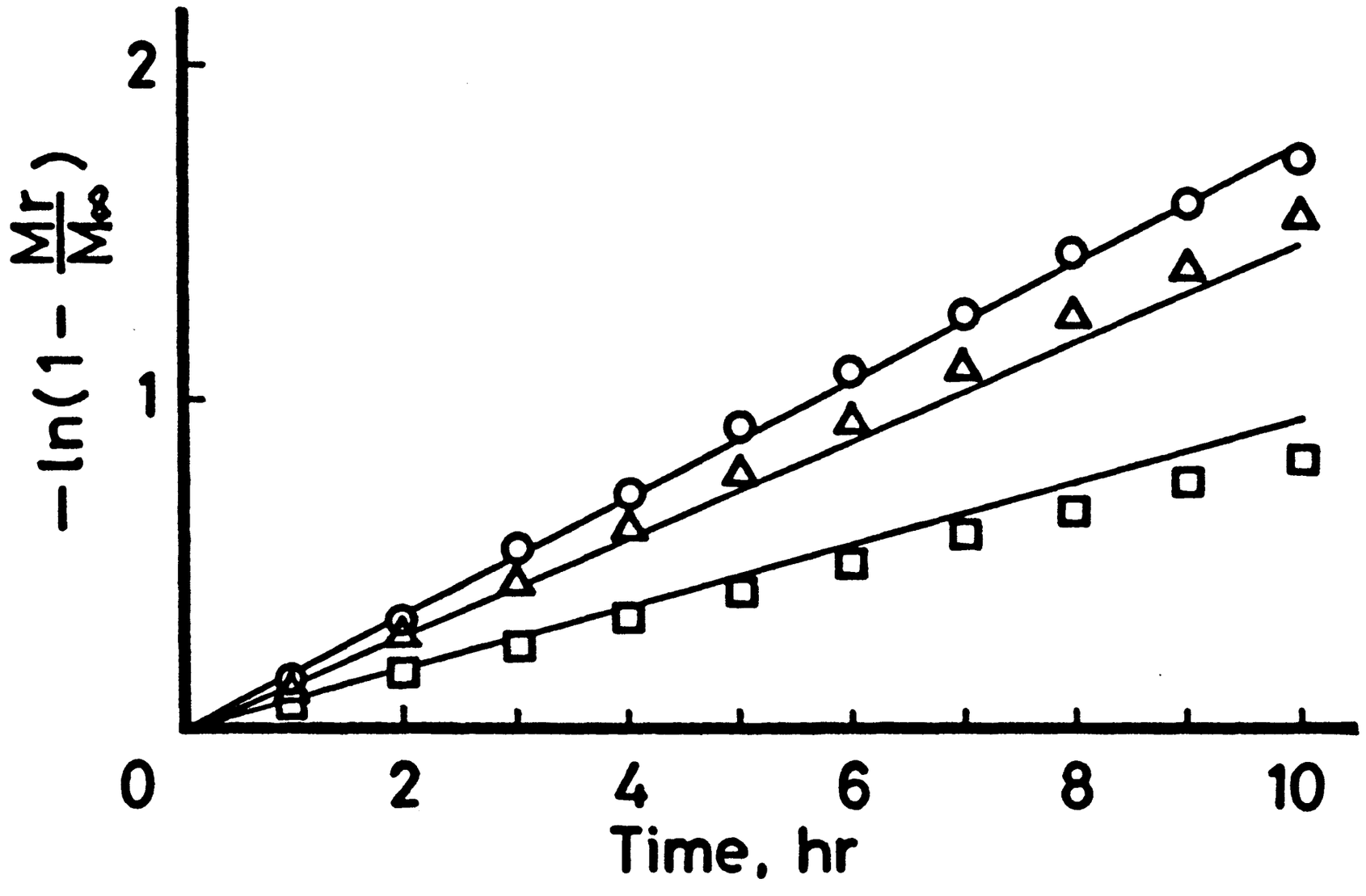

Figure 21. Release profiles of butamben through the silicone membrane (0.01 inch thick) from its initially saturated solutions in ○, 0.4% dodecyltrimethylammonium chloride; △, 0.5% polysorbate 80; and □, sodium dodecyl sulfate solution at 30°.
———, theoretical profile predicted from Eq. 16. Diffusion cell type 2 was used.

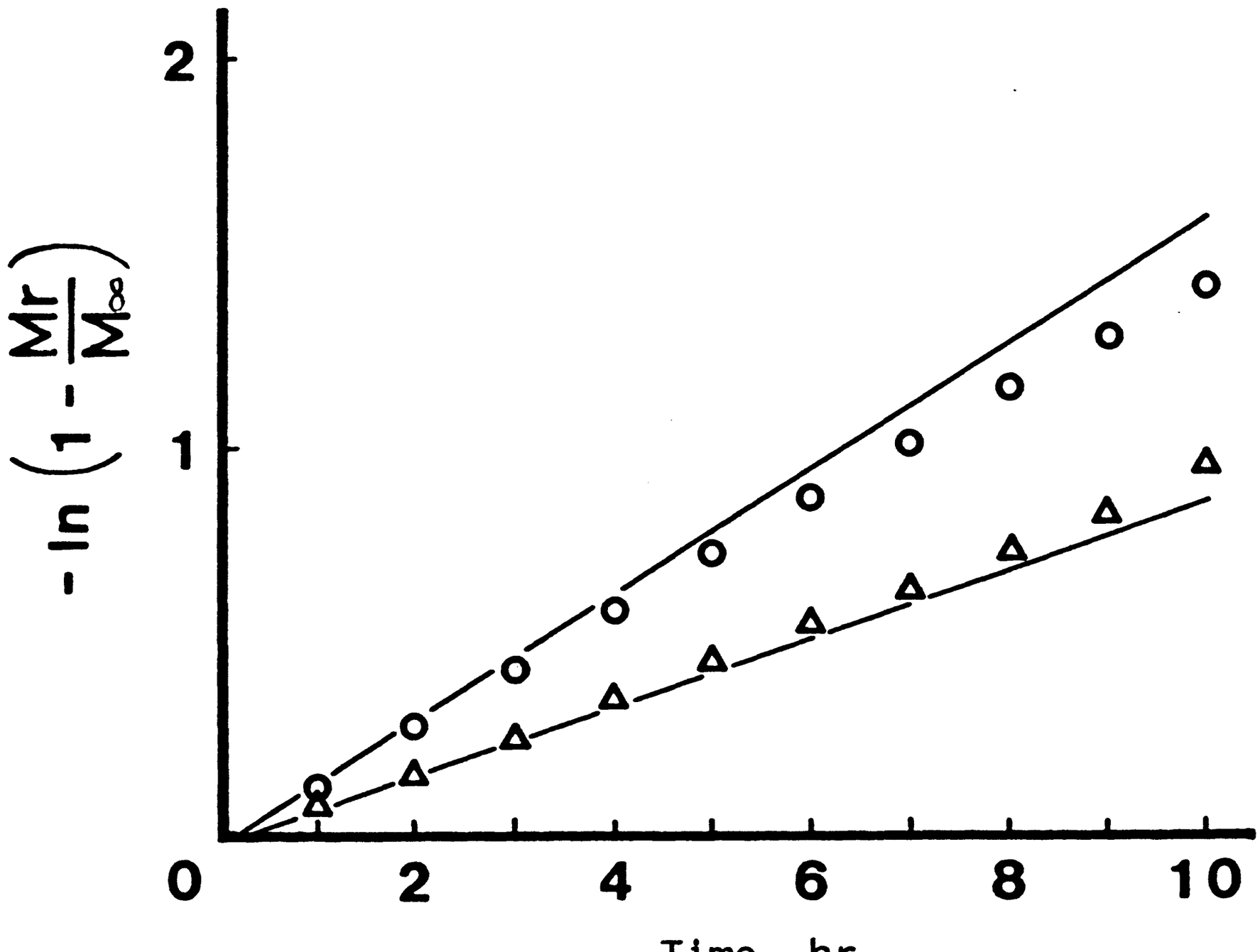

Figure 22. Release profiles of butamben through the silicone membrane (0.01 inch thick) from its initially saturated solutions in Δ, 0.5% laurylpyridinium chloride and O, 0.5% sodium dodecylbenzenesulfonate solution at 30°. ——, theoretical profile predicted from Eq. 16. Diffusion cell type 2 was used.

a certain error in determining the P value from suspension data or to an unidentified factor which was not taken into account in the model.

Benzocaine, an analog of butamben, was also employed to test the applicability of the model. Benzocaine has a higher solubility in water and a lower partition tendency to silicone membranes than butamben which was described previously. Fig. 23 shows the release profiles of benzocaine in the presence of two types of surfactants. Theoretical and experimental profiles coincided, indicating that the drug release in this case can be satisfactorily described by Eq. 16.

Fig. 24 represents data obtained with the ethylene-vinyl acetate copolymer membrane which is also classified as a partition membrane. Release of butamben through the ethylene-vinyl acetate copolymer membrane also followed the theoretical line.

When a suspension is employed as a donor solution, a dissolution step is involved as well as partition and diffusion steps. In such a drug as butamben which has a rather large (membrane/water) partition coefficient, dissolution may become a rate-determining step in some instances. If such be a case in the butamben-silicone membrane system, a calculated P value from permeation studies in the presence of suspensions may not represent a "true permeability". Slight deviation of the observed profile from the theoretical profile in the butamben-silicone membrane system may be attributable, in part, to this phenomenon. On the other hand, the permeation profile of butamben through an ethylene-vinyl acetate copolymer membrane and that of benzocaine

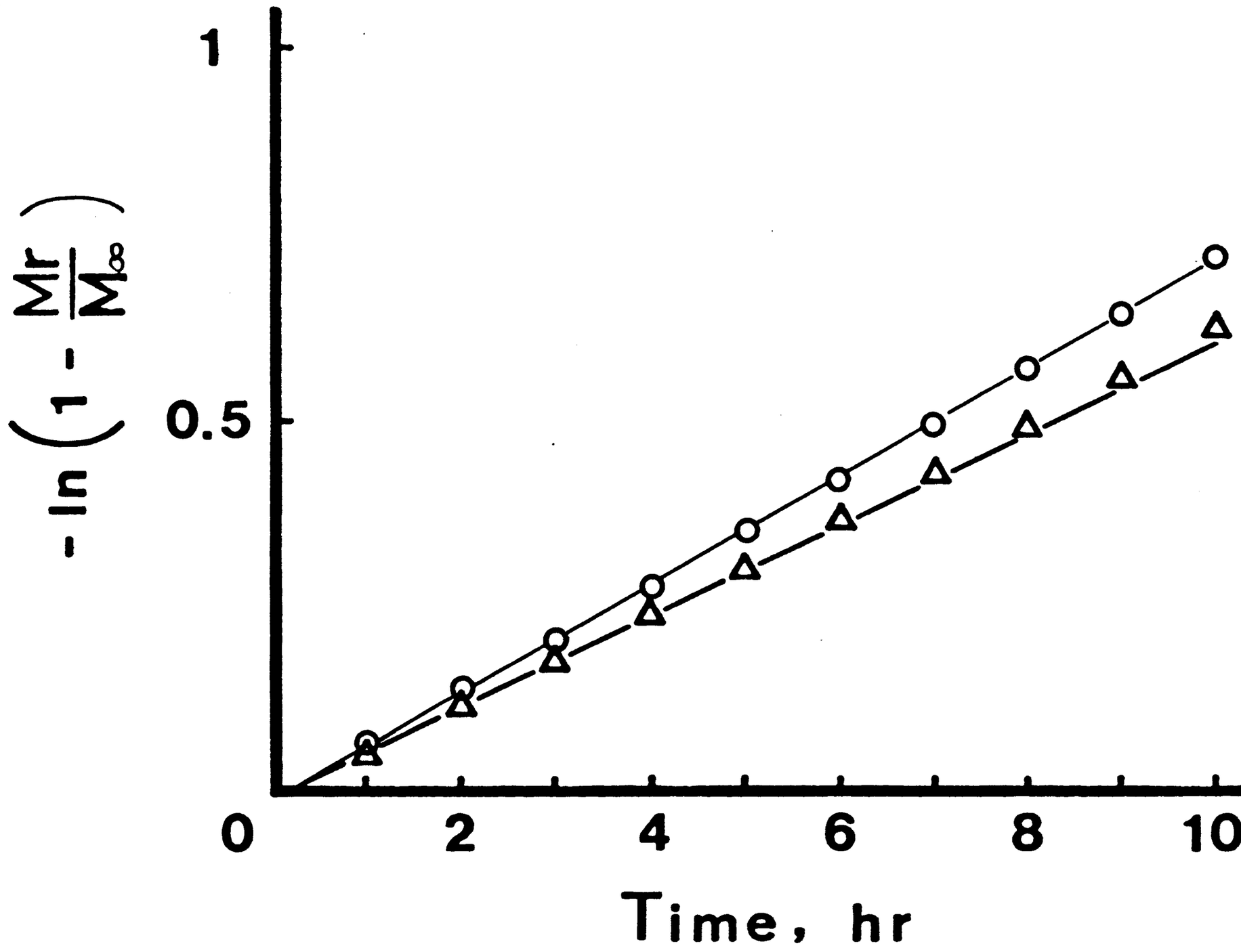

Figure 23. Release profiles of benzocaine through the silicone membrane (0.01 inch thick) from its initially saturated solutions in Δ, 0.5% dodecyltrimethylammonium chloride and O, 0.2% sodium dodecyl sulfate solution at 30°. ——, theoretical profile predicted from Eq. 16. Diffusion cell type 2 was used.

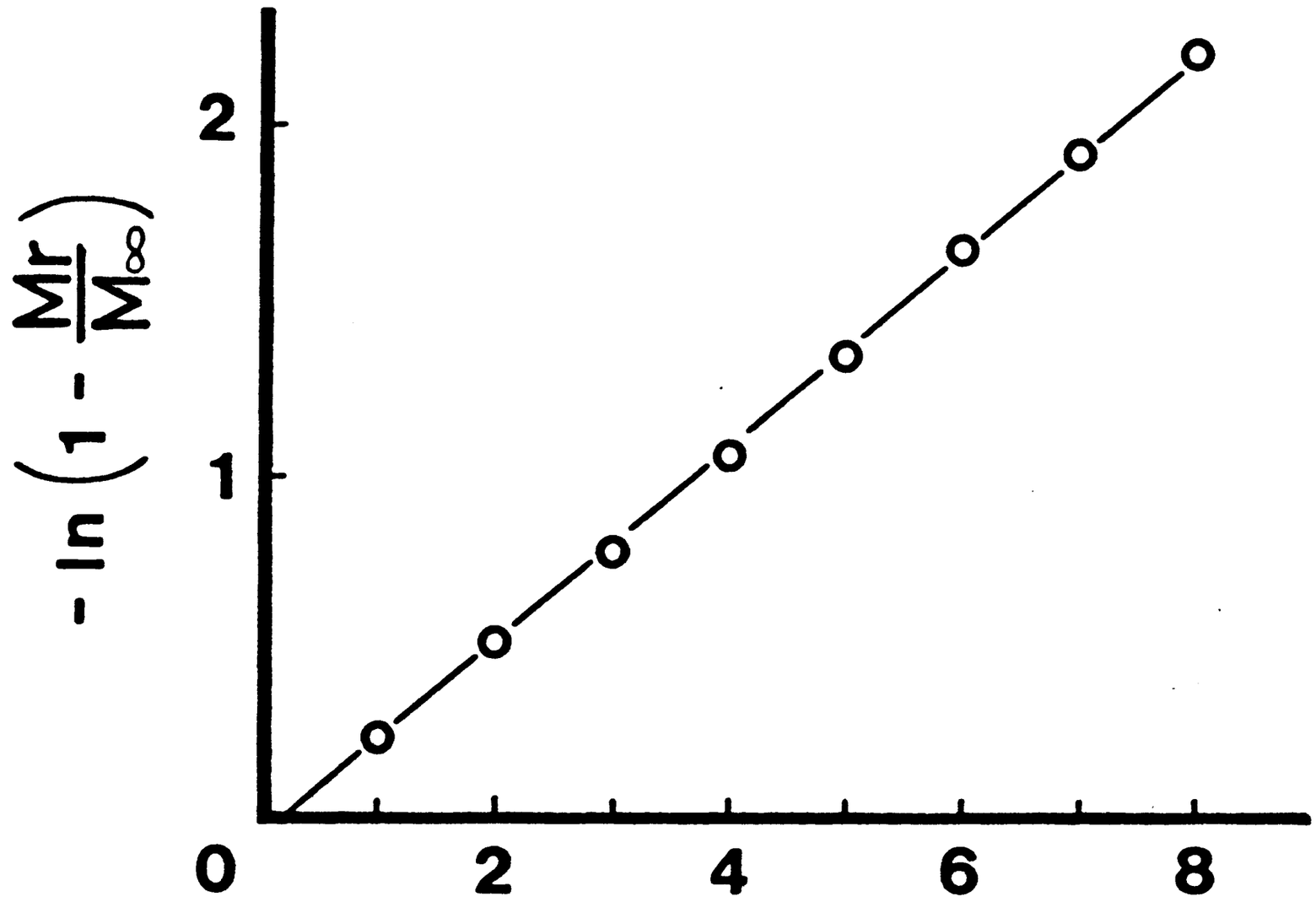

Figure 24. A release profile of butamben through the ethylene-vinyl acetate membrane (0.018 mm thick) from its initially saturated solution in 2% sodium dodecyl sulfate solution at 30°. ———, theoretical profile predicted from Eq. 16. Diffusion cell type 2 was used.

through a silicone membrane can be adequately described by the model (Figs. 23 and 24), indicating that a partition-controlled process is dominant in these systems. These observations may be rationalized in the following way. Since benzocaine has a lower partition coefficient than butamben and the ethylene-vinyl acetate copolymer membrane has lower permeability than silicone membrane (5.04×10^{-6} cm^2/sec, roughly, one half), partition of the drug into the membrane may become a rate-limiting step in these two cases.

From these results, the derived Eqs. 15 and 16 based on the proposed model shown in Fig. 4 are considered to adequately describe the release of drug through plane partition membranes from systems containing micelles.

Thus far, considerations have been on the systems of drug permeation through membranes in a plane sheet form. In addition to those systems, a system where the drug is released through a capsular (hollow cylinder) membrane, which is another practical dosage form, was also analyzed. As presented in the section of THEORETICAL CONSIDERATIONS, an equation was derived which may describe the release profiles of the drug from solutions containing micelles in capsules (Eq. 18).

In Fig. 25, release profiles of butamben from capsules (type 1) in the presence of 5 and 15% sodium dodecyl sulfate are shown along with theoretical curves predicted from Eq. 18. In the theoretical calculations, the following parameters were used: $P = 1.2 \times 10^{-5}$ cm^2/sec, $h = 3.1$ cm, $Cs^0 = 1.7 \times 10^{-6}$ $moles/cm^3$ at 37°, $V = 1$ cm^3, $r_o/r_i = 9.5/6.4$, and $Cs = 1.05 \times 10^{-4}$ and

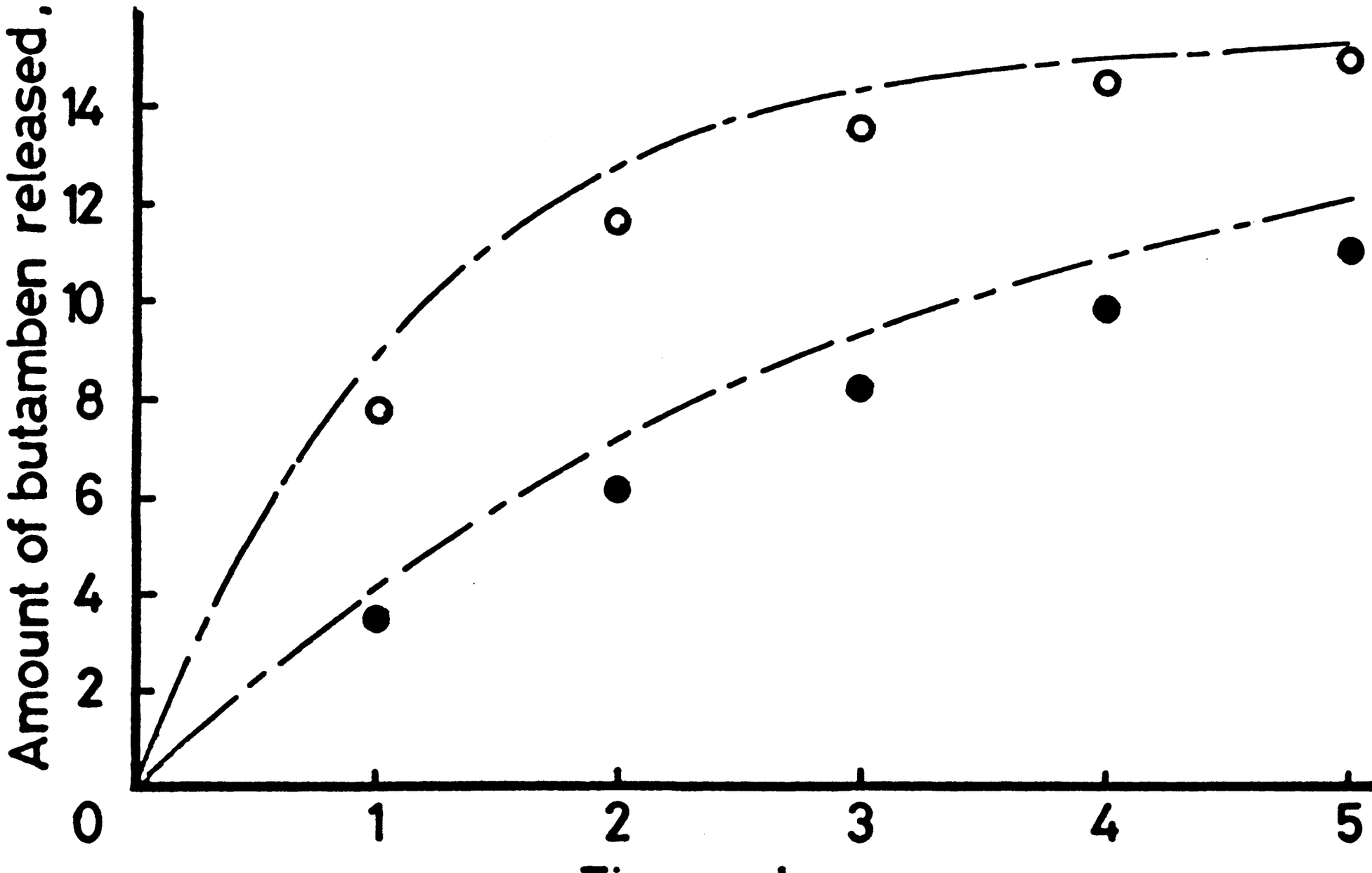

Figure 25. Release profiles of butamben from micellar systems at a drug loading of 15.5 mg in 5% (O) and 15% (O) sodium dodecyl sulfate solutions, in capsule type 1 at 37°. —·—, theoretical profiles predicted from Eq. 18.

2.9×10^{-4} moles/cm^3 in 5 and 15% sodium dodecyl sulfate solutions, respectively (determined at 37°), and M_∞ = 15.5 mg (loaded drug). As is seen in the figure, experimental data showed slower release rate than is predicted theoretically. The following interpretations may be made.

In the permeation experiments using the diffusion cells, solutions in both compartments were effectively stirred so that the thickness of a diffusion layer on the surface of the membrane is minimized and a concentration gradient is kept constant. In the permeation experiments using capsules, on the other hand, the donor (i.e. intracapsular) solution can not be stirred mechanically. Therefore, a contribution of a diffusion layer to the total release process may become apparent[78]. A poor correlation of the observed data with theoretical profiles in Fig. 25 may be due, in part, to the diffusion-layer effect.

In Fig. 26 are shown the same experimental data as that in Fig. 25 but with theoretical profiles predicted from Eq. 15. In the theoretical calculations, the following parameters were used: l = 0.155 cm (thickness of the capsule wall), A = 6.25cm^2 (inner surface area of the capsule), P, Cs^0, Cs, and V were the same as in the previous calculations. The observed data and the theoretical profiles coincided. Therefore, in this case, analysis of the release profiles on the basis of Eq. 15 gave a satisfactory approximation. The possible application of Eq. 15 to the capsular systems was further examined.

According to Eq. 15, Mr is expected to be proportional to M_∞. Shown in Fig. 27 are the release profiles of butamben

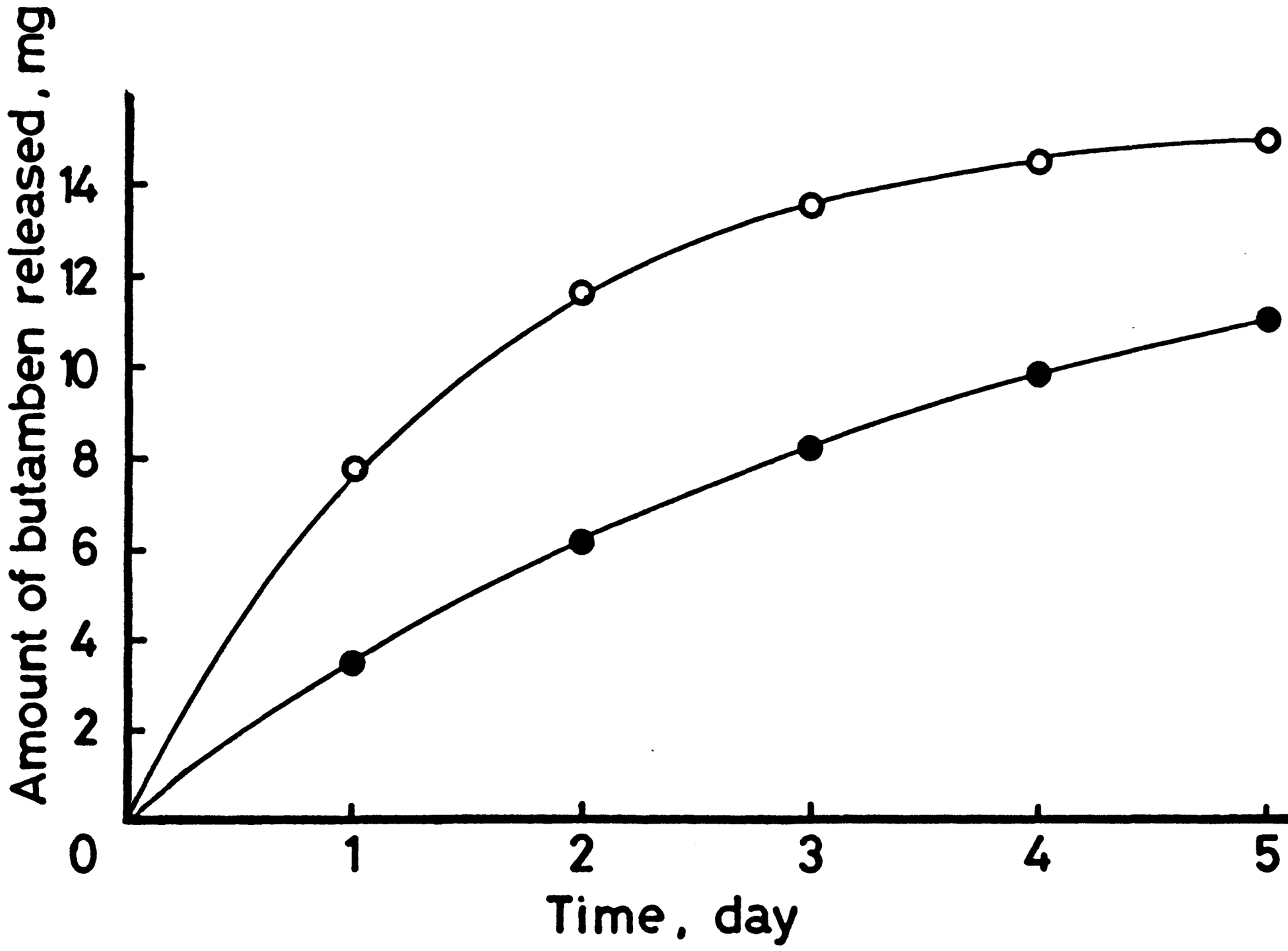

Figure 26. Release profiles of butamben from micellar systems at a drug loading of 15.5 mg in 5% (O) and 15% (O) sodium dodecyl sulfate solutions, in capsule type 1 at 37°. ——— , theoretical profiles predicted from Eq. 15.

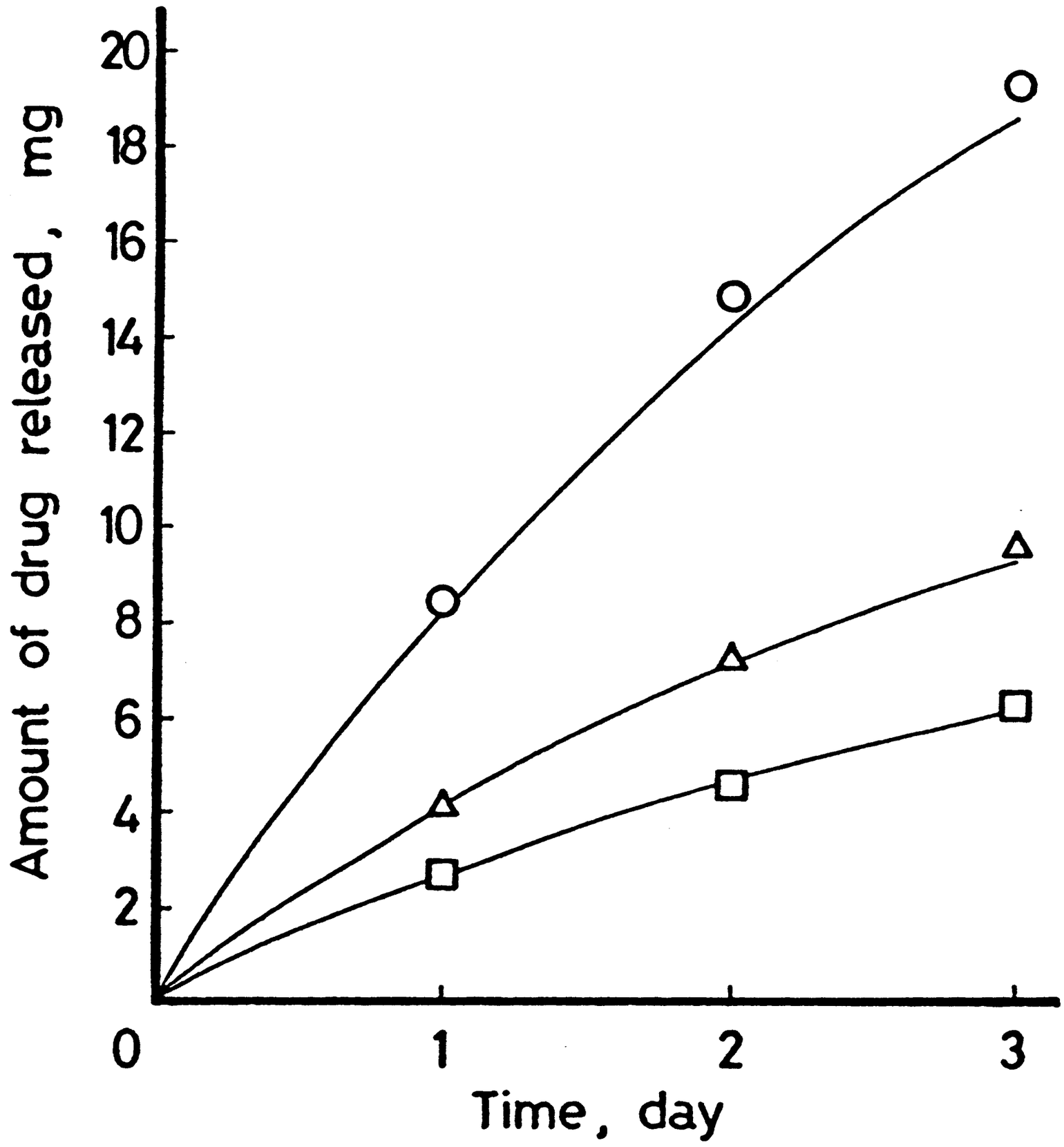

Figure 27. Release profiles of butamben from micellar systems in 10% sodium dodecyl sulfate solution at three loading levels in capsule type 1 at 37°C. Drug loading levels were O, 30 mg; Δ, 15 mg; and □, 10 mg. ——— , theoretical profile predicted from Eq. 15.

three drug loading levels along with theoretical curves predicted from Eq. 15. In this case, Cs = 2.27×10^{-4} moles/cm^3 (solubility of butamben in 10% sodium dodecyl sulfate solution at 30°). The observed profiles were very close to the curves theoretically drawn and the dependency of Mr on M_∞ is apparent. The parameter P is dependent on the polymeric material, while A, ℓ and V are dependent on the size of the device used. When M_∞ and these parameters are fixed, the release profile of the drug can be modified by the Cs term. A system having a large Cs value may be regarded as a large reservoir which functions to sustain the drug release. It is expected from Eq. 15 that doubling the value of Cs, for example, would lead to a two-fold increase in the time required to release the same amount of drug. The magnitude of Cs can be increased by increasing the concentration of surfactants or by employing a surfactant which solubilizes the drug more efficiently.

Shown in Fig. 28 is the effect of the surfactant concentration on drug release. Using the Cs values in 5, 10, and 15% sodium dodecyl sulfate solutions (previously shown in this section), theoretical release profiles were drawn according to Eq. 1, and a theoretical half-life (the time required to release one half of the drug incorporated) was calculated for each case. Calculated half-lives were 0.99, 2.14, and 2.74 days for the 5, 10, and 15% surfactant systems, respectively. Corresponding half-lives obtained from the data shown in Fig. 28 were 0.91, 1.84, and 2.72 days, respectively. Thus, a fairly good agreement was obtained between the theoretical values and experimental data.

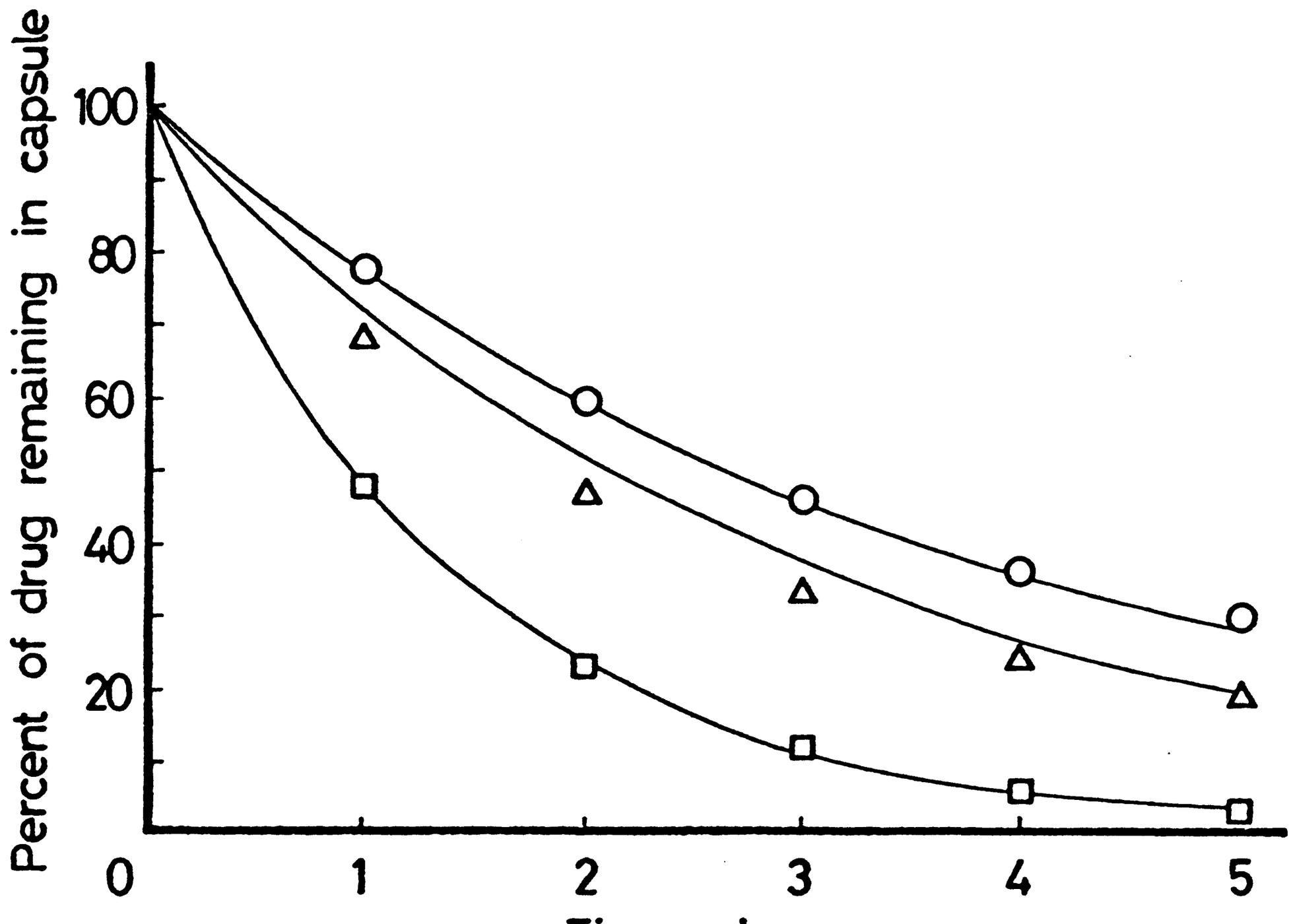

Figure 28. Effect of concentrations of sodium dodecyl sulfate on the release of butamben from micellar systems containing 15.5 mg of butamben in capsule type 1 at 37°C. Sodium dodecyl sulfate concentrations were O, 15%; Δ, 10%; and □, 5%. ———, theoretical profile predicted from Eq. 15.

Rlease profiles of the drug from slutions of two surfactants are compared in Fig. 29. Dodecyltrimethylammonium chloride solubilized butamben more than sodium dodecyl sulfate at an equal concentration (15%, in this case). Half-lives obtained from the data were 2.49 and 5.04 days for the sodium dodecyl sulfate and dodecyltrimethylammonium chloride systems, respectively. Thus, the drug release can be increasingly sustained by increasing the concentration of surfactants or by employing a surfactant with a higher solubilizing ability for the drug.

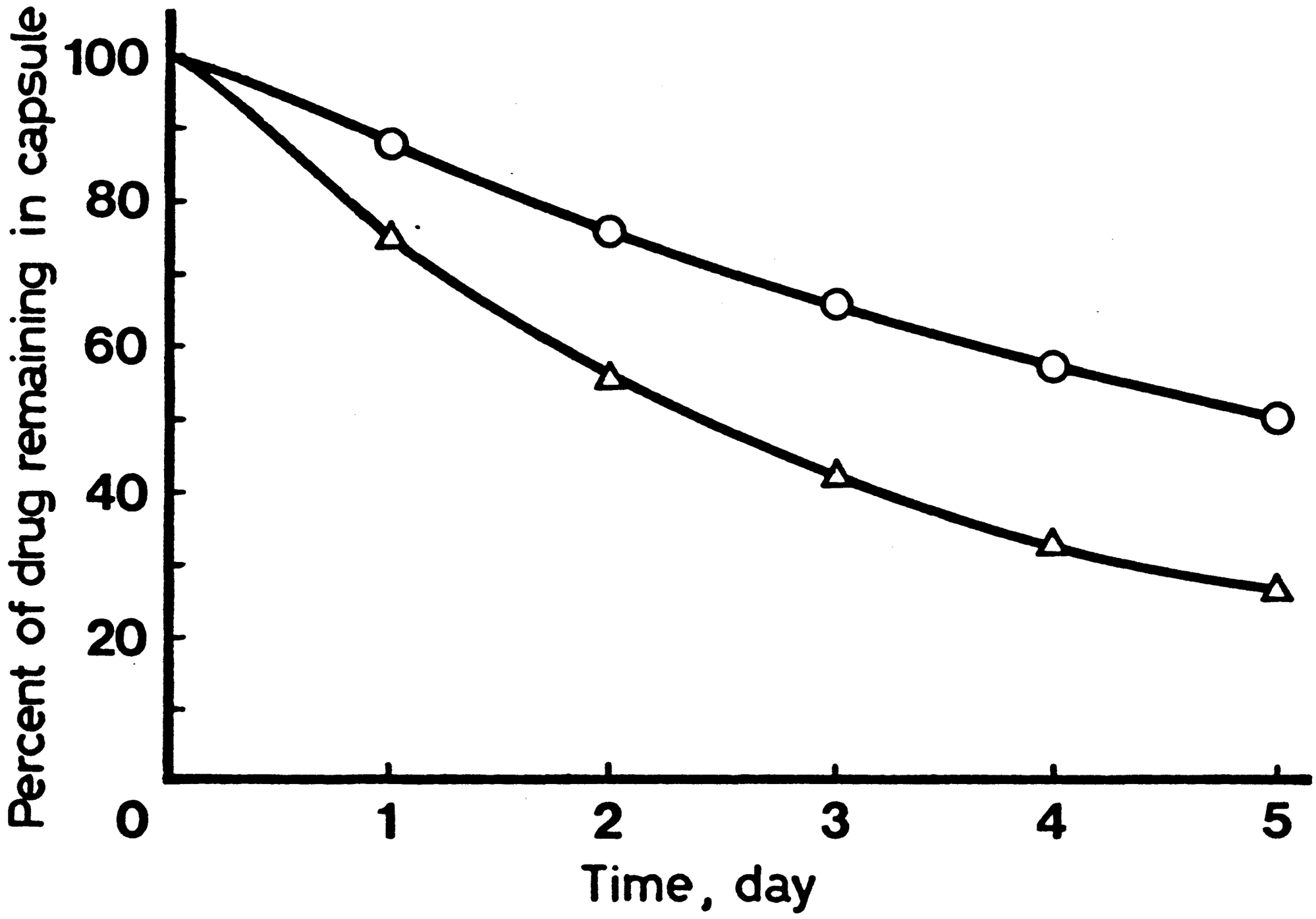

Figure 29. Release profiles of butamben from micellar systems in 15% surfactant solutions at a drug loading of 48.3 mg in capsule type 1 at 37°C. O, dodecyltrimethyl-ammonium chloride; Δ, sodium dodecyl sulfate.

4. Summary

Surfactants were examined for their possible role in sustaining drug release through a membrane. Three types of surfactants: anionic, cationic, and nonionic surfactants were investigated as to their solubilizing and release-sustaining behavior toward butamben. Among the three surfactants, dodecyltrimethylammonium chloride, a cationic surfactant, showed an excellent release-sustaining ability for the drug.

A theoretical model was introduced to describe the permeation of drug through membranes from systems containing micelles. Taking distribution of drug between aqueous and micellar phases into account, an equation was derived which describes the permeation profile of drug from the system. Applicability of the equation based on the proposed model was experimentally tested employing benzocaine as well as butamben, one of five surfactants, and silicone or ethylene-vinyl acetate copolymer membrane.
A fairly good agreement was obtained between the theoretical values and experimental data. Thus, the derived equation has proved to adequately describe the drug release from the system.

It was concluded that micelles serve as a large reservoir of drug and that the drug release can be increasingly sustained by increasing the concentration of surfactants or by employing a surfactant with a higher solubilizing ability for the drug. A desired release profile of drug can, therefore, be achieved by setting parameters properly on the basis of the model introduced. The possible application of surfactants to sustained-release systems was indicated.

PART IV: RELEASE OF BUTAMBEN FROM COSOLVENT SYSTEMS

1. Solubilization of Butamben in Cosolvent Systems [46)]

Shown in Fig. 30 is the solubility diagram of butamben in the macrogol 400-water mixture. The solubility of butamben was enhanced remarkably by an increase in the macrogol fraction and the semilogarithmic plot gave a straight line which is in consistent with that theoretically predicted by Eq. 19 (see experimental section). For the macrogol fraction up to 0.5, the solubility of butamben can be described by a specific form of Eq. 19 using Cs^0 = 1.7 mM = 1.7×10^{-6} moles/cm^3 (solubility of butamben in water at 37°) and σ = 3.445 moles (slope of the line in Fig. 30):

$$\log Cs' = \log (1.7 \times 10^{-6}) + 3.445 \cdot f \qquad \text{(Eq. 29)}$$

where Cs' = the solubility of butamben in the binary solvent of the W/V fraction f of macrogol 400 at 37°. This system is considered to possess a reservoir function for the drug because of the increased solubility of the drug.

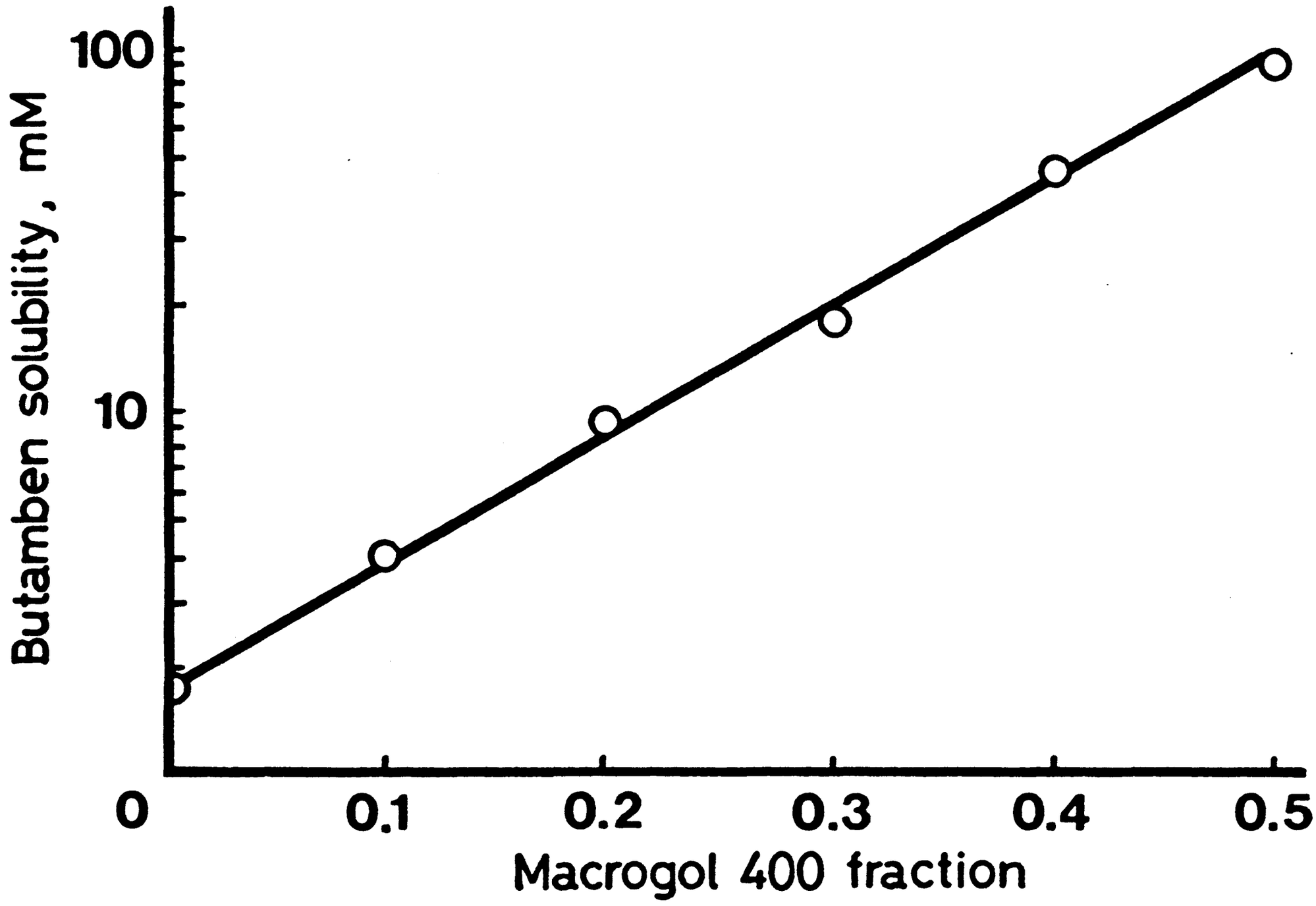

Figure 30. Relationship between solubility of butamben and the W/V fraction of macrogol 400 at 37°.

2. Release Profiles of Butamben from Cosolvent Systems[46)]

Shown in Fig. 31 is the effect of the macrogol fraction (up to 0.5) on butamben release from capsules. In the profile, a lag time of 8.2 to 13.3 min was observed, with the average being 11.4 min. As the macrogol fraction is increased , the fractional release rate (defined as the release rate divided by the loading of the drug) became smaller and the release profile approached a zero-order release pattern. From the initial steady-state portion of the profiles, the release rate constant was calculated and plotted against the macrogol fraction (Fig. 32). The release rate constant decreases linearly with the macrogol fraction. This provides a means of controlling the drug release rate employing the cosolvent system.

The effect of molecular weight of the cosolvent on the drug release was also examined (Fig. 33). Macrogol 400 and macrogol 20000 gave comparable release profiles. Therefore, the effect of molecular weight of the cosolvent, if any, was considerably small.

In Fig. 34, the theoretical release profiles predicted from Eq. 27 and Eq. 28 for these systems are shown. The fractional release rate obtained in the experiments in each case was much smaller than that predicted theoretically. That difference among them are possibly due to some contribution of diffusion layer-effect. Thus, in this case, the release profile of butamben from the cosolvent systems through a silicone capsular membrane has proved not to be wholly described by a simple membrane-limited release model[80)]. However, the data shown in Fig. 32 would provide one a meaningful information for the controlled drug release.

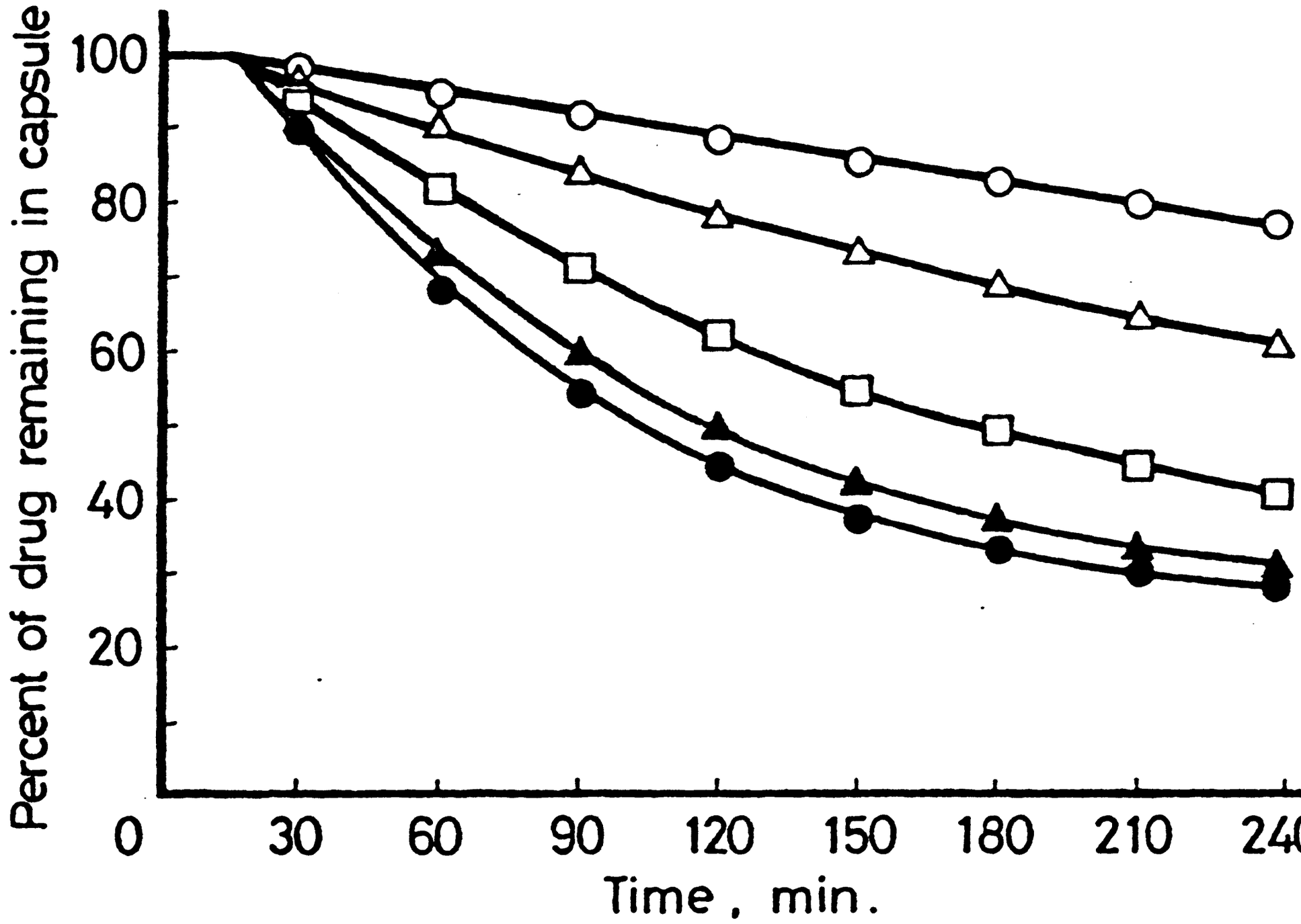

Figure 31. Effect of the fraction of macrogol 400 on the release of butamben from macrogol 400-water mixtures containing butamben at half its solubility, in capsule type 2 at 37°C. The W/V fractions of macrogol 400 were ○, 0.5; △, 0.4; □, 0.3; ▲, 0.2; ●, 0.1.

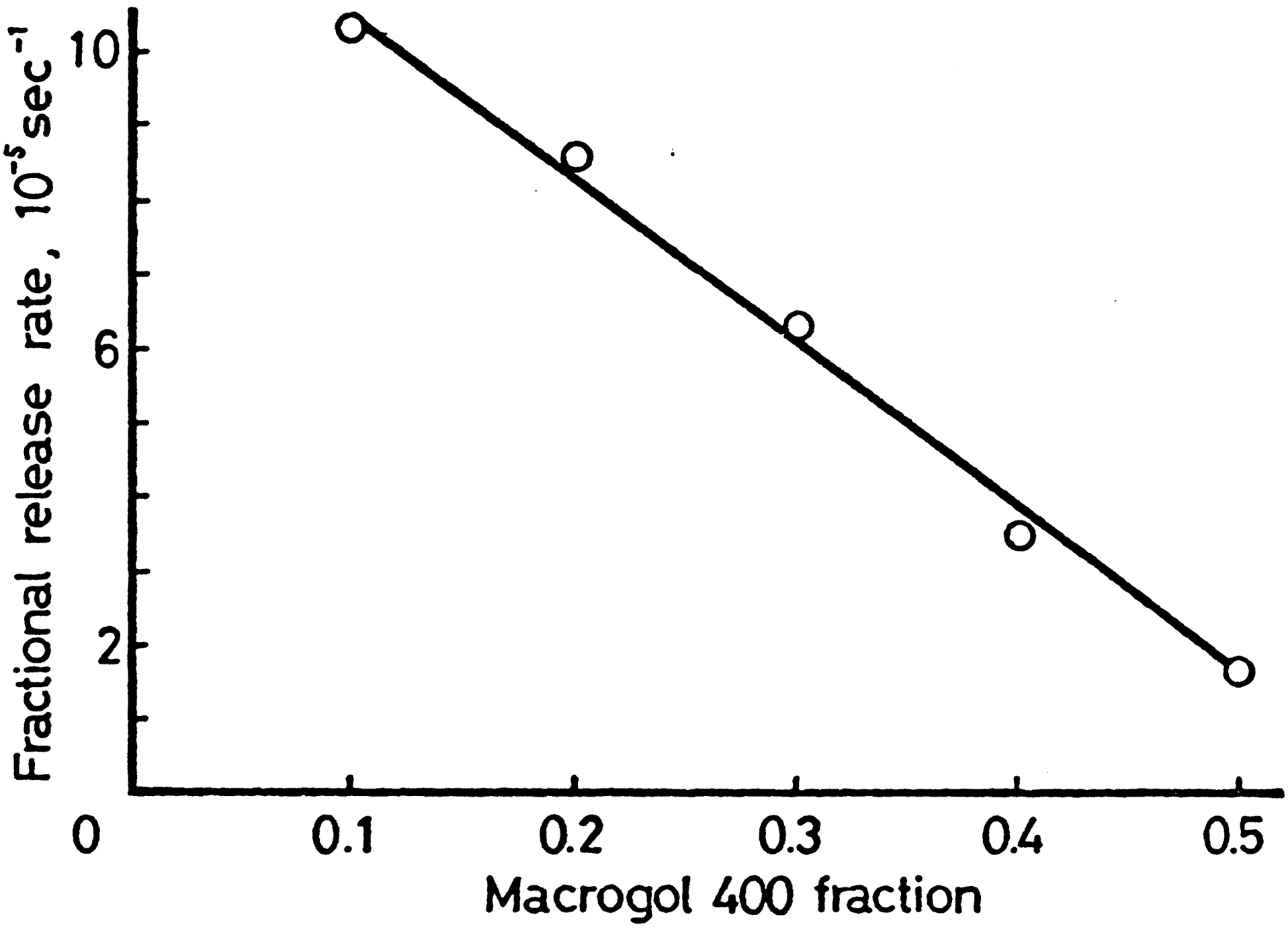

Figure 32. Effect of the W/V fraction of macrogol 400 on the initial fractional release of butamben from macrogol 400-water mixtures containing butamben at half its solubility, in capsule type 2 at 37°C.

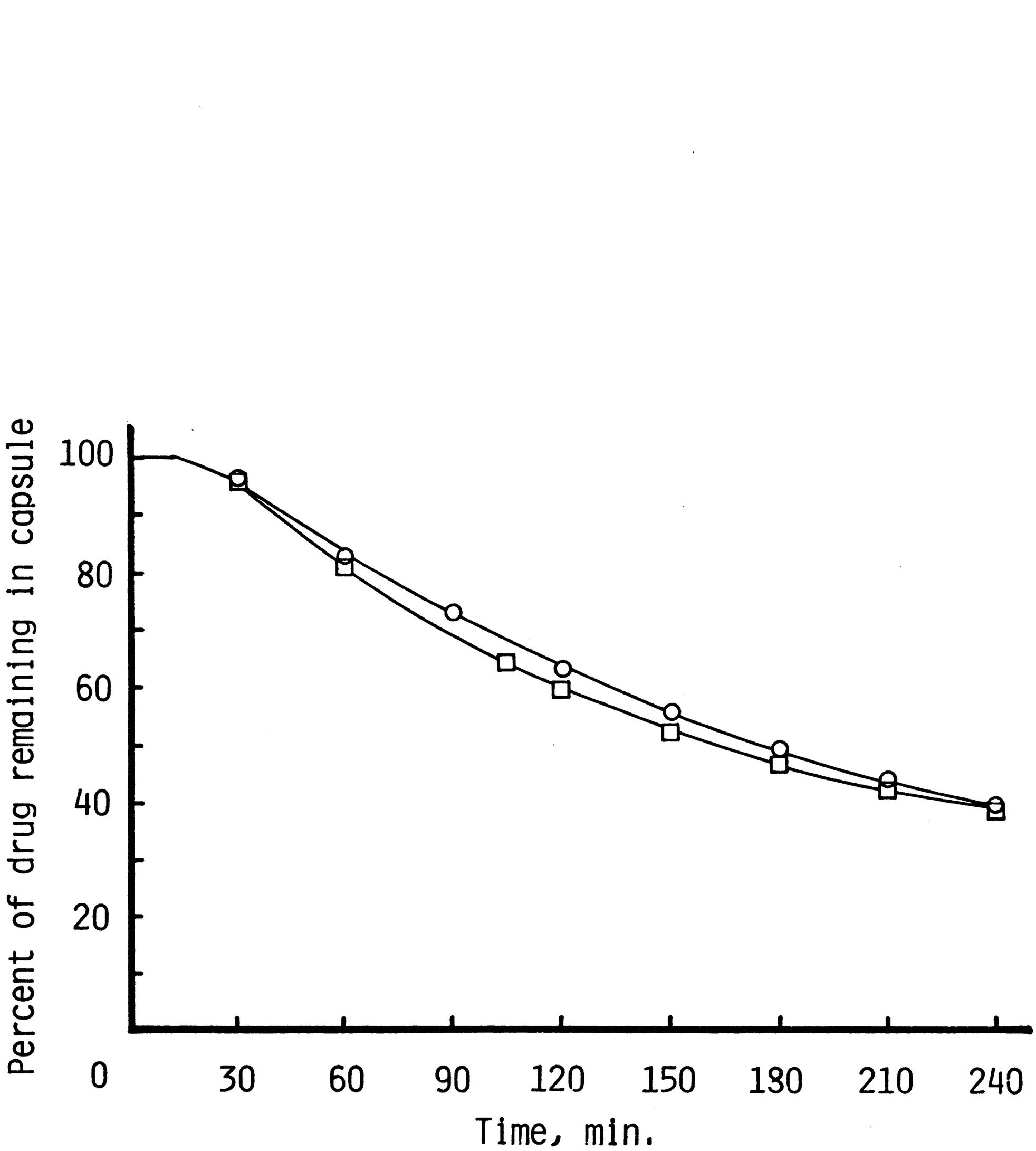

Figure 33. Effect of the molecular weight of macrogol on the release of butamben from macrogol-water mixtures of the macrogol fraction of 0.3 containing butamben at half its solubility, in capsule type 2 at 37°.
The molecular weights were □, 400 and O, 20000.

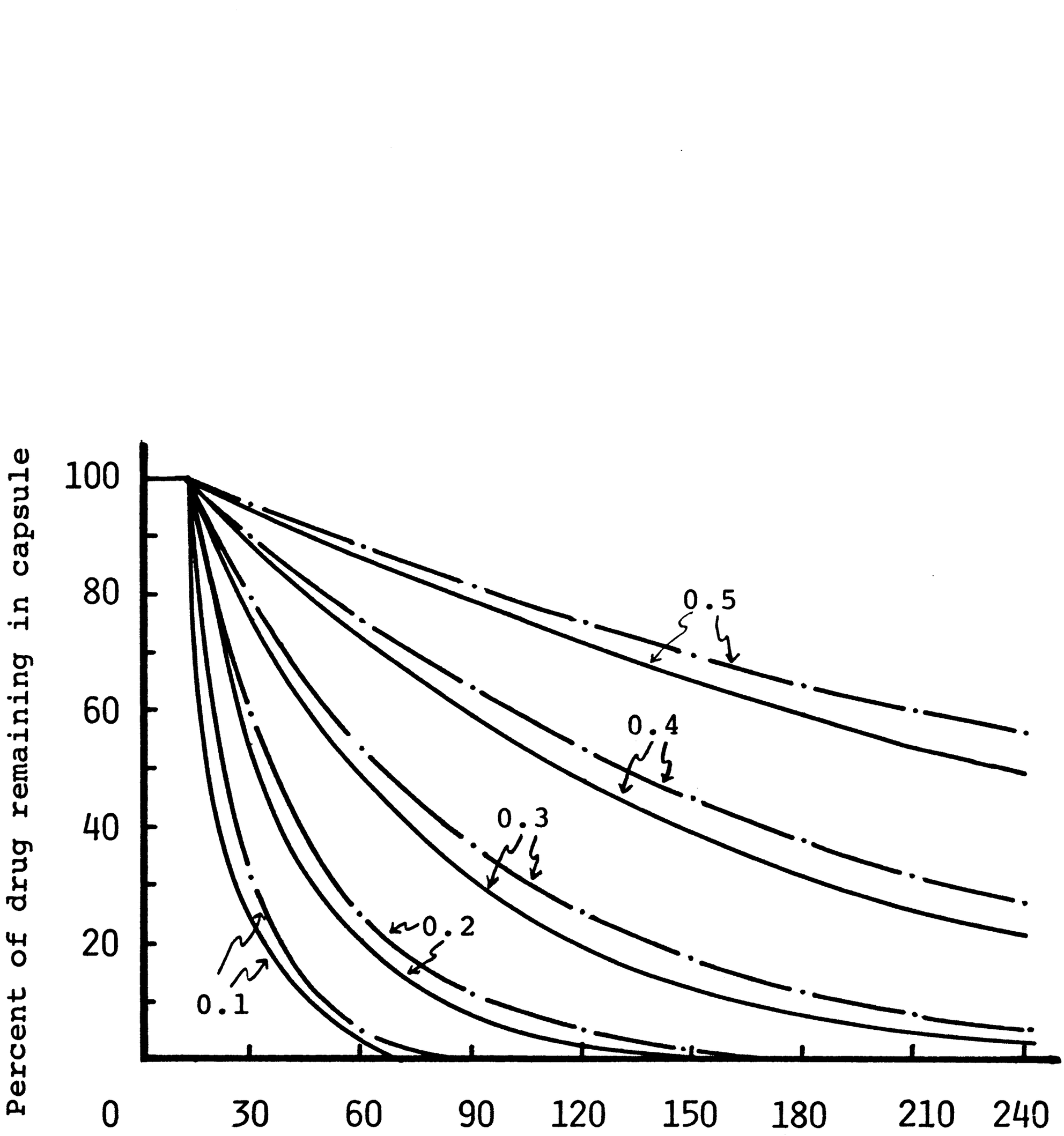

Figure 34. Theoretical release profiles of butamben from macrogol 400-water mixtures with various fractions of macrogol 400, in capsule type 2 at 37°. Each number indicates the fraction of macrogol 400.
—·—, predicted from Eq. 27 and ——, from Eq. 28.

3. Summary

Cosolvent systems, macrogol 400-water mixtures, were evaluated for their possible use as drug reservoirs to control or to sustain the drug release through a membrane. The solubility of butamben was increased exponentially with the cosolvent (macrogol) fraction. The fractional release rate of butamben through a silicone capsular membrane decreased linearly with the cosolvent fraction. Thus, the release of butamben was more sustained by employing a vehicle (solvent mixture) of higher fractions of the cosolvent. Because of the high stability and solubilizing ability for the drug, the cosolvents may be conveniently applied for the controlled and sustained drug release systems.

PART V: RELEASE OF BUTAMBEN FROM OIL-IN-WATER TYPE EMULSION[46)]

The physical stability of several preparations was investigated prior to the release studies. Various degrees of phase separation were observed in a 5-day period in the emulsions with low contents of sodium alginate and oils. The emulsion prepared with 0.5 ml of the oil containing 48.3 mg of the drug and 0.5 ml of aqueous solution containing 0.4% polysorbate 80 and 2.0% sodium alginate did not show any noticeable phase separation in 5 days.

The release of butamben from this emulsion was examined and the results are shown in Fig. 35. The release pattern (solid line) was almost the same as that obtained when the micellar solution of 15% sodium dodecyl sulfate with the same drug loading was used (dotted line). In emulsions, much drug can be incorporated into the oil phase so that a sustained release is achieved.

In this experiment, the size of the oil droplets in the formulated emulsion was not measured. If permeation through the membrane is the slower process, and hence the rate-determining step, the release rate is not expected to be influenced by droplet sizes. Although this assumption may have to be examined when emulsion droplets of larger sizes are employed. Since emulsions are physically unstable in contrast with micellar solutions or cosolvent systems, its applicability to a general use may be limited.

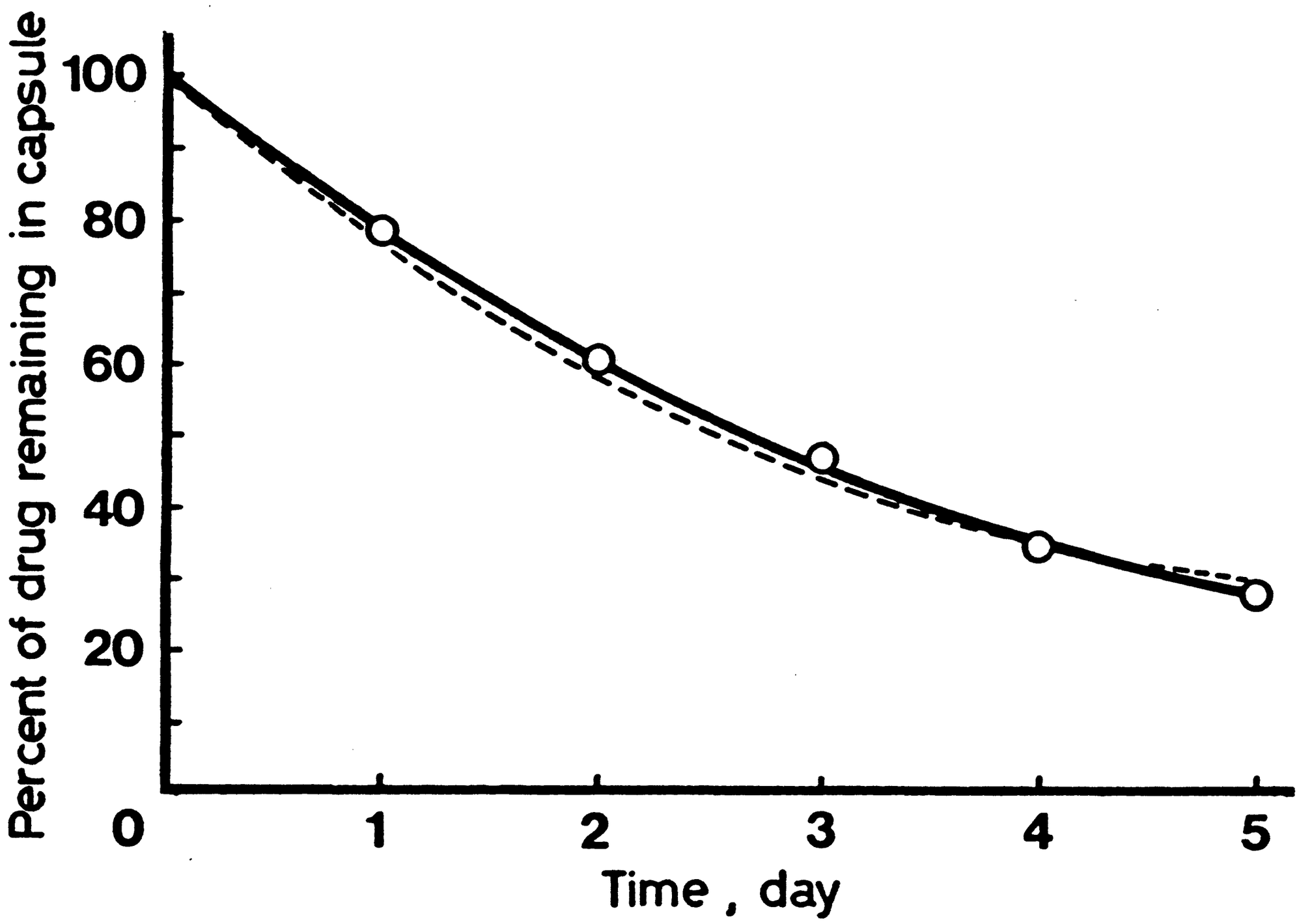

Figure 35. Comparison of the release profile of butamben from the emulsion system (solid line) with that from the micellar system in 15% sodium dodecyl sulfate solution (dotted line) at a drug loading level of 48.3 mg in capsule type 1 at 37°. The emulsion was formulated with 0.5 ml of cotton seed oil containing the drug and 0.5 ml of an aqueous solution containing 0.4% polysorbate 80 and 2.0% sodium alginate.

PART VI: CORRELATION OF RELEASE PROFILES IN VITRO WITH RELEASE DATA IN VIVO[46)]

In developing a sustained drug release system for a given drug, the in vitro-in vivo correlation of both the mechanisms and the rates of drug release should be evaluated. The information thus obtained can then be appllied to studies to further develop a system that delivers the drug at a programmed rate for an optimum duration of treatment. As an initial evaluation of the systems that have been described in the present work, release experiments in vivo were carried out.

In Fig. 36, the release of butamben from capsules implanted subcutaneously in rabbits is shown together with release data in vitro. Correlations of drug release from topical delivery systems in vitro with that in vivo have been reported: some of which are good, some are poor[81-84)]. In spite of some possible differences between the environments surrounding the capsules in the in vitro and in vivo experiments, a very close agreement was found in the release rates between the two studies. In order to compare these quantitatively, the data were analyzed on the basis of Eq. 16.

A plot of $-\ln\left\{1 - (Mr/M_\infty)\right\}$ against time should give a straight line with a slope of $APCs^0/\ell VCs$. The slope thus obtained was used to compare the release pattern. The data for release studies in vitro and in vivo are shown in Fig.37. In both cases, straight lines with similar slopes (1.60×10^{-6}/sec in vitro, 1.63×10^{-6}/sec in vivo) were obtained. No significant difference was found in the release profile of butamben from silicone rubber

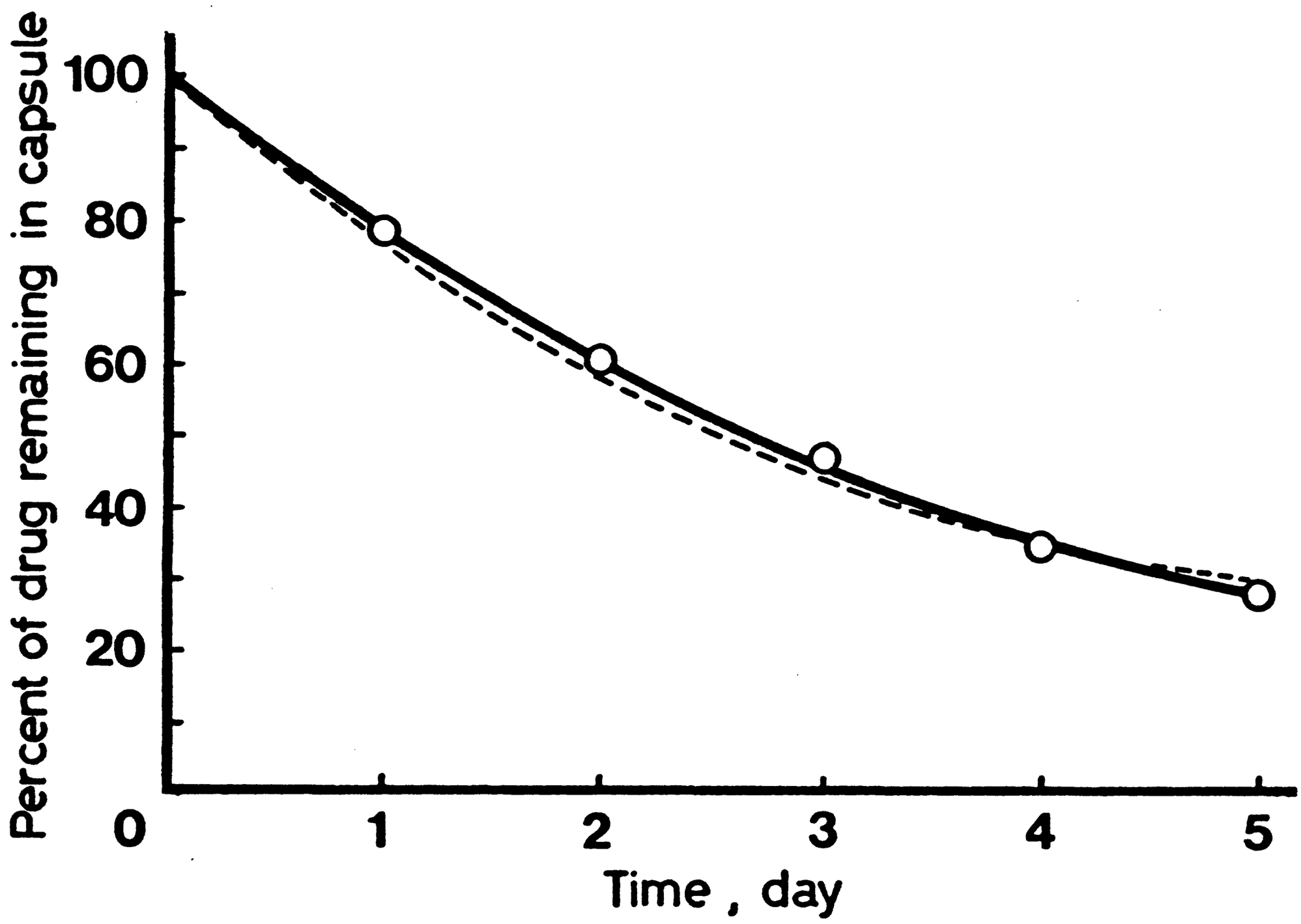

Figure 35. Comparison of the release profile of butamben from the emulsion system (solid line) with that from the micellar system in 15% sodium dodecyl sulfate solution (dotted line) at a drug loading level of 48.3 mg in capsule type 1 at 37°. The emulsion was formulated with 0.5 ml of cotton seed oil containing the drug and 0.5 ml of an aqueous solution containing 0.4% polysorbate 80 and 2.0% sodium alginate.

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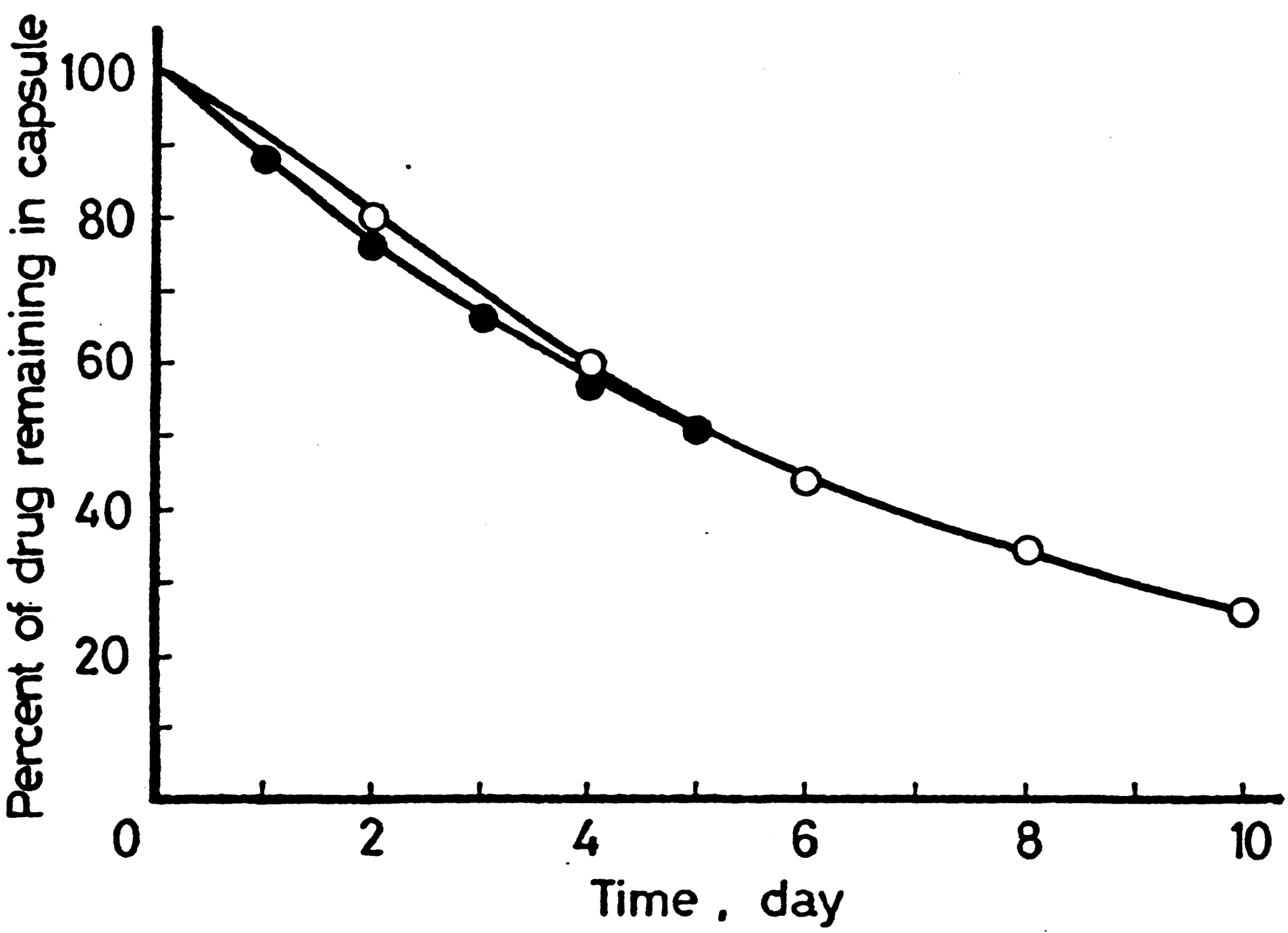

Figure 36. Comparison of the release profile of butamben from the micellar system in 15% dodecyltrimethylammonium chloride solution at a drug loading level of 48.3 mg in capsule type 1. ●, in vitro at 37°; O, in vivo.

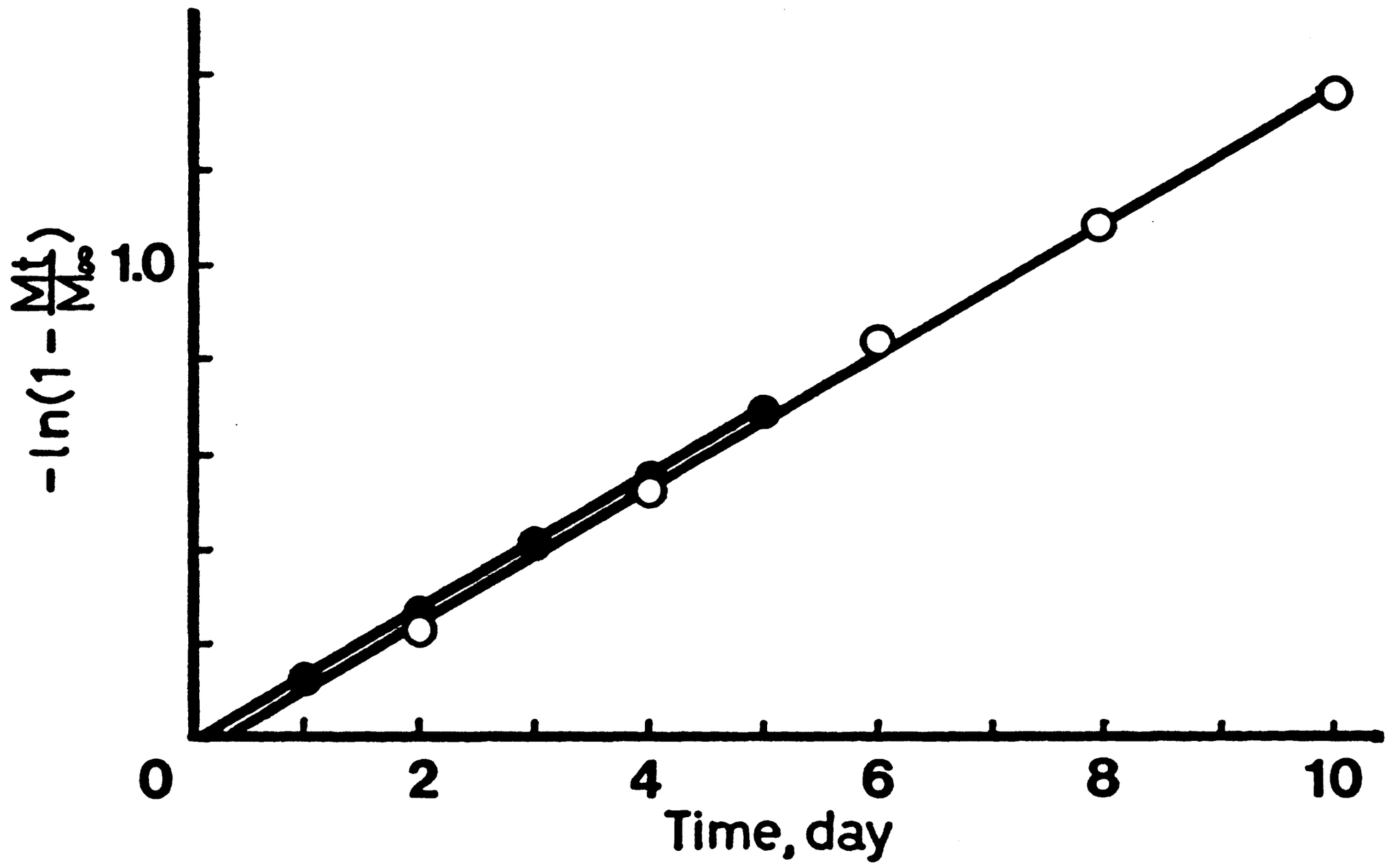

Figure 37. Linear presentation of the data shown in Figure 36.

capsules between the two studies. Although release studies in vivo were investigated only for the micellar system, the close agreement between the release in vitro and in vivo would also be expected for the other systems included in this work, since permeation through the silicone rubber membrane appeared to be the rate-limiting step and no accumulation of the released drug around the capsule would be expected.

Comparative studies indicated that the drug release in vitro agrees well with that observed in vivo. Therefore, an initial design of a controlled release device may be made on the basis of in vitro experiments.

CONCLUDING REMARKS

Controlled drug delivery systems have widely received attentions for their promising development in drug therapy. Several systems developed to date have found their preferable use in titrating diseases more effectively over conventional methods, although they are still open to further improvement. One of the most accesible and promising strategy for the systems is the use of polymeric substances. Since polymers have a variety of characteristics and are capable of (physico-)chemical modifications, their limitless use is expected.

When a drug delivery system using polymers is considered, a proper choice of a drug, a polymer substance as well as geometry of the system is essential to achieve a desired drug delivery. In the studies presented herein, possible control of drug release through a polymer membrane by means of "solution reservoir" of the drug was introduced and evaluated for its applicability. Soluble complexes of the drug, micelles, cosolvents, and oil-in-water type emulsions were examined for their reservoir functions to control or sustain the release of local anesthetics through silicone membranes.

From the results obtained in the present investigations, the following conclusions can be drawn:

1) Among the local anesthetics examined, butamben is a good choice in the systems in which a partition membrane such as a silicone membrane plays a role of a release-rate-limiting barrier.

2) If systems are capable of forming soluble, membrane-imperme-

able complexes, the release of the drug from the systems can be sustained than that from the plain solution of the drug, although never exceeding that from the suspension in water. Control of the release profile of drug between these limits is possible by means of a proper choice of complexing agents. The more stable the complex is, the slower is the initial rate of release but the longer is the time required for complete release.

3) Surfactant solutions can retain drugs in solution to a great extent due to micellar solubilization and thus serve as a large reservoir of the drug. Greater release rate and longer duration of release can be achieved by a proper selection of surfactants. Release profiles of the drug from the systems can be adequately described quantitatively, hence, predictable.

4) Cosolvents also provide solution reservoir systems, and cosiderably sustained release of the drug is obtained when cosolvent systems with large fractions of the nonaqueous cosolvent are employed.

5) In emulsions, much drug can be incorporated into the oil phase so that sustained release is obtained. The general use of emulsions may be limited because of their poor physical stability.

6) Comparative studies indicated that the drug release in vitro agrees well with that observed in vivo. Therefore, an initial design of a controlled release device may be made on the basis of in vitro experiments.

Thus, those solution reservoir systems described can be usefully applied to the drug delivery systems in combination with a proper choice of a drug or a membrane material as well as a geometry of the system.

SCOPE

In the present work, a silicone rubber membrane was selected as a release-rate-limiting barrier for the drug. Because of the well documented biocompatibility, silicones are being widely used for medical purposes. For example, silicones are used in artificial lungs, heart valves, pace-makers, and other artificial organs. If necessary, drugs can be impregnated in the polymer from which they are released to exert antiinflammatory, antiinfective or immunosuppresive actions.

A silicone elastmer is classified as a "biostable" polymer. The elastmer is less susceptible to any chemical and/or physical changes. More recently, biodegradable polymers have been introduced to the drug delivery systems. Following a hydrolytic or enzymatic degradation of the polymers containing drugs within the body, concomitant drug release can be obtained. Such systems should be prepared from toxicologically acceptible components.

The means for sustaining release of drugs as those described in the present work may be extended to the biodegradable drug delivery systems which are composed of biodegradable polymers, toxicologically acceptible additives such as natural surfactants, and the drug.

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