Controlled Drug Permeation I: Controlled Release of Butamben through Silicone Membrane by Complexation

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Abstract □ The effects of caffeine, β-cyclodextrin, and povidone on the permeation behavior of butamben from saturated solutions in these complexing agents through a dimethyl polysiloxane membrane were investigated at 30°. In all systems, these agents increased the rate of release over the plain saturated drug solution. The effect was more pronounced with caffeine and β-cyclodextrin than with povidone. Interpretation of these results with the aid of solubility data for the corresponding systems led to the following generalization. For a fixed total (free and complexed) amount of drug available for release, sustained release is associated with systems containing more stable complexes. The practical value of this approach to the controlled release of drug is discussed.

Keyphrases □ Butamben—controlled release from saturated solutions through silicone membrane, effect of caffeine, β-cyclodextrin, and povidone as complexing agents □ Membrane permeation—controlled release of butamben from saturated solutions through silicone membrane, effect of caffeine, β-cyclodextrin, and povidone as complexing agents □ Drug delivery systems—controlled release of butamben from saturated solutions through silicone membrane, effect of caffeine, β-cyclodextrin, and povidone as complexing agents □ Complexation—effect of caffeine, β-cyclodextrin, and povidone on controlled release of butamben through silicone membrane □ Silicone membrane—controlled release of butamben, effect of caffeine, β-cyclodextrin, and povidone

Controlled release[1] of drugs has received much recent attention from the standpoint of increasing the effectiveness and decreasing the side effects in long-term administration of therapeutic agents (1). 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 systems is a capsule of polymeric material filled with the drug in a solid or liquid state or with a suspension or solution of the drug in a fluid. The release of the drug is controlled by diffusion through the capsule walls.

To achieve constant release from a drug delivery system, the concentration gradient has to be maintained constant. A constant concentration gradient may be achieved by having either: (*a*) a large volume reservoir of drug in the solution (2) or (*b*) the drug in the solid phase (3) in the donor side of a membrane and a sink condition in the receptor side. Because of the difficulty in accommodating a large volume reservoir within the drug delivery system, suspensions are usually employed to maintain the drug concentration within the delivery system constant.

Suspensions, however, have their own problems such as sedimentation and particle-size growth of the dispersed solid during storage. Therefore, the possible use of complexation as the reservoir was examined as a way to sustain drug release over a specified period.

Complexation in pharmaceutical systems has been studied by many workers (4). Its possible role in accelerating or retarding drug permeation[1] through a silicone membrane has been reported (5, 6). In the present studies, the effects of three types of complexes on the permeation of a local anesthetic, butamben, were investigated. The complexes included were: (*a*) plane to plane, (*b*) inclusion, and (*c*) macromolecular.

Caffeine has been reported to form complexes with aromatic molecules, presumably of plane-to-plane stacking (7). β-Cyclodextrin, on the other hand, has been known to include drug molecules within its cavity (8). Povidone, a water-soluble polymer, has been studied as to its complexing tendencies with drugs (9).

THEORETICAL

When the transfer of drug from a donor solution to a receptor solution is considered (Fig. 1), Fick's law of diffusion may be written in the following form:

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

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

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

$$\frac{dM_t}{dt} = DA\frac{C_{m,d} - C_{m,r}}{l} = DA\frac{K_dC_d - K_rC_r}{l} \qquad \text{(Eq. 2)}$$

where $C_{m,d}$ and $C_{m,r}$ = drug concentrations in the membrane at the donor side and receptor side, respectively; K_d and K_r = distribution coefficients of the drug between the membrane and the donor solution and the membrane and the receptor solution, respectively; C_d and C_r = 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, C_r remains negligible compared to C_d. Then Eq. 2 can be simplified to:

$$\frac{dM_t}{dt} = \frac{DAK_d}{l}C_d = \frac{PA}{l}C_d \qquad \text{(Eq. 3)}$$

where $P = DK_d$ = permeability.

Case 1 (Zero-Order Release)—When a suspension is placed at the donor side, 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 (Fig. 1, Case 1). Equation 3 is then written:

$$\frac{dM_t}{dt} = \frac{DAK_d}{l}C_s \qquad \text{(Eq. 4)}$$

where C_s = solubility of the drug in the donor solution. Since all terms on the right-hand side of Eq. 4 are constant, the release rate of drug through the membrane is constant. A plot of the release rate against time gives a straight line parallel to the time axis (Fig. 2, Case 1).

Case 2 (First-Order Release)—When a plain saturated drug solution is placed in the donor compartment, the drug concentra-

[1] In this paper, "permeation" and "transport" refer to three successive processes of partition into, diffusion through, and partition out of the membrane, whereas "release" refers to the last process.

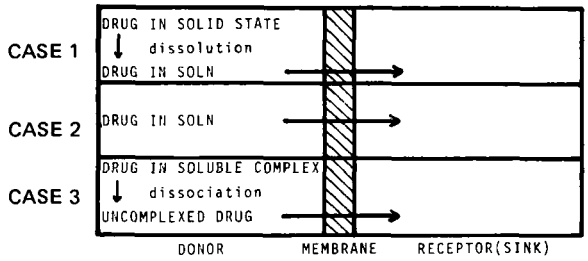

Figure 1—*Schematic representation of the permeation of drug from three different conditions (Cases 1–3) in the donor compartment.*

tion in the donor solution decreases with time as the drug permeates to the receptor solution (Fig. 1, Case 2). Under this condition, Eq. 3 becomes:

$$\frac{dM_t}{dt} = \frac{DAK_d}{l} C_s e^{-(DAK_d/lV)t} \qquad \text{(Eq. 5)}$$

where V = volume of the donor solution. Thus, the release rate plotted against time yields an exponential curve (Fig. 2, Case 2).

Case 3—When a saturated drug solution containing a complexing agent is placed in the donor compartment, the complexed drug may serve as a reservoir. Loss of uncomplexed (permeable) drug from the donor solution by permeation is partly compensated for by dissociation of the complex (Fig. 1, Case 3). Therefore, the concentration of permeable drug does not decrease as rapidly as in the plain solution (Case 2).

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. A plot of the release rate against time gives a curve falling between a straight line (zero-order release) and an exponential curve (first-order release) (Fig. 2, Case 3).

EXPERIMENTAL

Materials—Medical grade dimethyl polysiloxane sheeting[2] in a labeled thickness of 5 mil (0.127 mm) was used. The following chemicals were obtained from commercial sources and used after characterization by differential scanning calorimetry and thermal gravimetric analysis but without further purification: butamben[3], reagent grade, mp 56.5°; benzocaine[4], Japanese Pharmacopeial grade, mp 89.0°; methylcellulose 4000 cps[5]; caffeine monohydrate[5], reagent grade; β-cyclodextrin[6]; and povidone[7].

Test Solutions—Solutions used in permeation studies were prepared in the following fashion. A suspension was prepared in a water-jacketed beaker maintained at 30° by stirring an excess amount of the local anesthetic in water or in 0.1% methylcellulose solution for 2 days with a magnetic stirrer. Saturated solutions were prepared similarly by stirring an excess of the local anesthetic in various vehicles and filtering through a sintered-glass disk just prior to diffusion studies.

Permeation Studies—The quasisteady-state diffusion cell previously described (5) was used. The cell was initially equilibrated overnight in a shaker bath maintained at 30° with 50 ml of distilled water in both arms. Water was removed by suction; 40 ml of 0.1 N HCl (to maintain a sink condition with respect to the permeable species in the receptor solution by protonating the permeated local anesthetic) was added to one arm, and an equal volume of a test solution was pipetted into another arm. All 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. With the suspension of drug in water only, 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 local anesthetic was measured at 287 nm.

[2] Silastic nonreinforced, lot HH0842, Dow Corning, Midland, Mich.
[3] Tokyo Kasei, Tokyo, Japan.
[4] Torii Pharmaceuticals, Tokyo, Japan.
[5] Wako Pure Chemical Industries, Osaka, Japan.
[6] CPC International, Englewood Cliffs, N.J.
[7] K15, Daiichi Pure Chemicals, Tokyo, Japan.

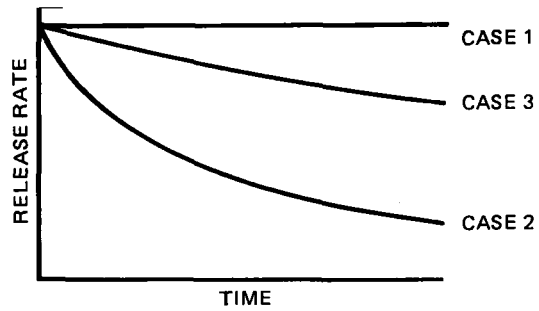

Figure 2—*Illustration of the time dependence of release rate for the three cases: 1, suspension; 2, saturated solution in water; and 3, saturated solution in solutions of complexing agents.*

Determination of Solubility—An excess of the local anesthetic was placed into each vial containing a complexing agent at various concentrations. The vials were then equilibrated at 30° by shaking for at least 24 hr. In the β-cyclodextrin system, where a complex with limited solubility was formed, a longer equilibration period (3 days) was required. Equilibrated mixtures were filtered quickly, and the filtrates were assayed for the local anesthetic as follows.

Analytical Methods—*Spectrophotometric Assay*—In the absence of any interfering material, the UV absorbance of butamben at 287 nm was used to determine the concentration of the local anesthetic that permeated into the receptor solution. The solubilities of the local anesthetic were similarly determined.

GLC Assay—In the presence of UV-absorbing interfering material (caffeine), the concentration of butamben was determined by GLC. A known amount of benzocaine (internal standard) was added to a sample solution, and water was vacuum evaporated. The residue was subsequently dissolved in 50 μl 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[8]; column, 2-m stainless steel with 1.5% OV-101 on Shimalite W (80–100 mesh)[5]; injection port temperature, 265°; column 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.

RESULTS AND DISCUSSION

Permeation behaviors of butamben from the suspensions in water and methylcellulose solution, from its saturated solutions in 2% solutions of various complexing agents, and from the plain saturated solution (no solid nor complexing agent) are shown in Fig. 3. When the suspensions were placed in the donor compartment, the concentration of drug in the receptor solution increased linearly with time, since a concentration gradient was maintained constant.

Although the solubility of the drug in 0.1% methylcellulose was the same as in water, the release rate of the drug was smaller from the methylcellulose suspension than from the propeller-stirred suspension in water, indicating that the better dispersion and reduced diffusion layer thickness around the solid in the latter favor the dissolution of the drug which, in turn, favors the transport of the drug. When the saturated solution was used as a donor 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 2% complexing agents were used, the release curves 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 the effects of complexation on permeation are considered, it is appropriate 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 *Theoretical* section. Among the

[8] Shimadzu GC-4APF, Shimadzu Manufacturing Co., Kyoto, Japan.

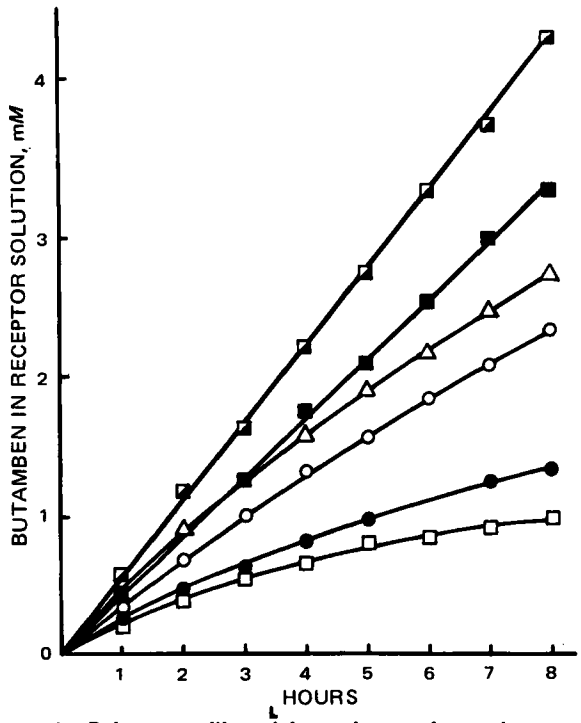

Figure 3—*Release profiles of butamben under various conditions. Key: ◪, suspension in water stirred by propeller; ■, suspension in 0.1% methylcellulose; △, saturated solution in 2% caffeine; ○, saturated solution in 1.1% β-cyclodextrin (see text); ●, saturated solution in 2% povidone; and □, saturated solution in water.*

complexing agents employed in this study, β-cyclodextrin and povidone are not expected to permeate through the membrane because they do not partition into the membrane. Caffeine, on the other hand, permeates very slowly. However, its much smaller permeability ($P = 8 \times 10^{-9}$ cm²/sec) (5) in comparison with that of butamben ($P = 6 \times 10^{-6}$ cm²/sec) warrants the assumption that the caffeine concentration in the donor solution remains essentially constant throughout the permeation study.

As for the permeation of the complexed species, the cyclodextrin and povidone complexes can be considered impermeable since these complexing agents do not partition into the silicone membrane. If the caffeine complex had permeated at a significant rate, the initial release rates of butamben from the caffeine system would have been much greater than those from the drug suspension, since six times as much drug is present in the caffeine system as in the saturated solution. This, however, was not the case. The permeability of the caffeine–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.

To gain insight into the influence of the degree of complexation on the permeation pattern of the drug, the solubilities of the drug in solutions of the complexing agents were also measured (Fig. 4). Solubility increased linearly with the concentration of caffeine and povidone, whereas β-cyclodextrin formed a complex with limited solubility (the solubility of the complex was about 7 m*M* at 30°). Stability constants calculated by the Higuchi and Connors equation (4) were 2.2×10^3, 61, and 2.9 M^{-1} for β-cyclodextrin, caffeine, and povidone (where the repeating unit was taken to be its molecular weight), respectively.

Figure 4 also provides information concerning the exact amounts of the free and complexed drug present in the donor solution of the three systems at zero time. At zero time, the amount of the free drug was the same in all systems. The drug solubilized by each 2% 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 saturated solution in water, was much smaller than in the other two systems.

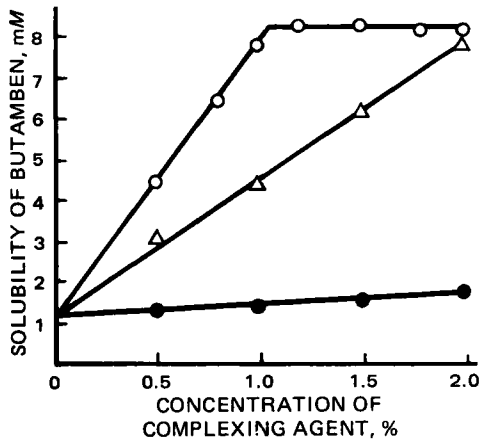

Figure 4—*Solubility profiles of butamben in solutions of three types of complexing agents. Key: ○, β-cyclodextrin; △, caffeine; and ●, povidone.*

With the β-cyclodextrin system, the donor solution at zero time contained only 1.1% total β-cyclodextrin instead of 2%; the difference, having precipitated as the solid complex, was removed from the system upon filtration. The total drug (free and complex) in the donor solution at zero time was estimated to be 0.33 mmole from the solubility diagram (Fig. 4). In the 2% caffeine system, the total drug was estimated similarly to be 0.31 mmole. Therefore, in these two systems, the total amount of drug available for permeation was comparable even with different stability constants. Consequently, if the permeation studies (Fig. 3) were continued to infinite time, the permeation profiles for these two systems would have converged to similar plateaus.

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. 3 for the first 8-hr period clearly indicate that the rate of release was initially smaller

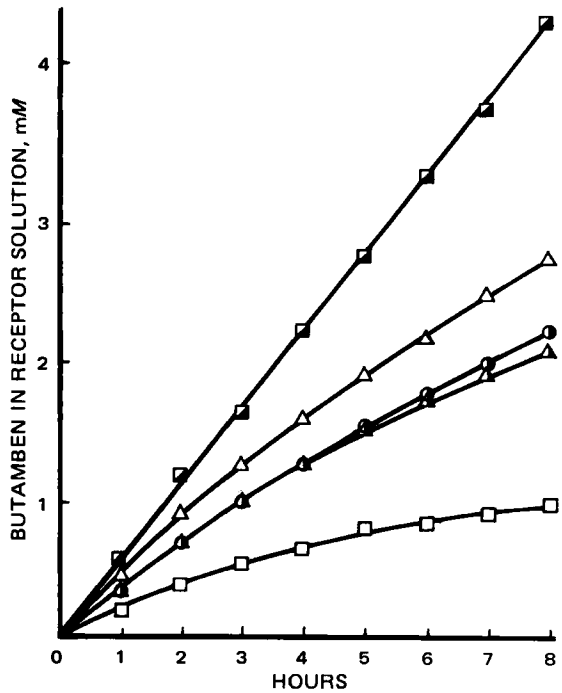

Figure 5—*Release profiles of butamben under various conditions. Key: ◪, suspension in water stirred by propeller; △, saturated solution in 2% caffeine; ◑, saturated solution in 1% β-cyclodextrin, ▲, saturated solution in 1% caffeine; and □, saturated solution in water.*

from the β-cyclodextrin system than from the caffeine system. Since the total drug available for release in these systems was comparable, the rate of release in the caffeine system must have declined faster than in the β-cyclodextrin system.

To confirm the present interpretation, the permeation study was repeated using the saturated solution of the drug in 1% β-cyclodextrin (Fig. 5). At this concentration, the solubility of the complex was not exceeded. As can be seen from Fig. 5, the total amount of the drug available for permeation was equal to that of the previously studied permeation from the saturated solution of drug in 2% caffeine (*i.e.*, 0.31 mmole). Therefore, the permeation profiles presented in Fig. 5 for the 2% caffeine system and the 1% β-cyclodextrin system should have a common plateau. If so, the faster initial rate of release in the 2% caffeine system must lead to a shorter release time than in the 1% β-cyclodextrin system. The following generalization may, therefore, be made. For a fixed amount of total (free and complexed) drug, the more stable the complex is, the greater is the tendency of the system to sustain the release of drug; *i.e.*, the release of drug extends over a longer period.

The permeation profile from 1% caffeine is also shown in Fig. 5. Since the amount of total drug in 1% β-cyclodextrin was greater than that in the 1% caffeine system (Fig. 4), 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.

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 a fixed amount of total drug (*i.e.*, fixed amount of complex since free drug is independent of the complexing agent), the more stable the complex is, the slower is the initial rate of release but the longer is the time required for complete release. 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 drug in solution.

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Tritiated Naltrexone Binding in Plasma from Several Species and Tissue Distribution in Mice

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Abstract □ The binding of 15,16-^{3}H-naltrexone in human, monkey, dog, guinea pig, rat, and mouse plasma was investigated over a range of concentrations, including predicted therapeutic levels. Studies using equilibrium dialysis at 37° indicate that the extent of binding is independent of naltrexone concentration over the concentration range of 1–500 ng/ml for dog plasma and of 0.1–500 ng/ml for human, monkey, guinea pig, rat, and mouse plasma. The extent of naltrexone binding in plasma is similar in the six species studied, the range being from 20% bound in rat plasma to 26% in plasma from beagle and mongrel dogs. This relatively low extent of naltrexone binding in plasma is consistent with previous findings of a large apparent volume of distribution for this drug in the dog. To investigate further the distribution of tritiated naltrexone, the tissue levels of radioactivity in mice at 1, 5, and 15 min after intravenous administration of 8-^{3}H-naltrexone were determined. Naltrexone was rapidly distributed from plasma to tissues, with less than 4% of the dose being present in plasma at 1 min after injection.

Keyphrases □ Naltrexone—plasma protein binding in humans, monkeys, dogs, guinea pigs, rats, and mice, tissue distribution in mice □ Protein binding, plasma—naltrexone, humans, monkeys, dogs, guinea pigs, rats, and mice □ Distribution, tissue—naltrexone, mice □ Pharmacokinetics—naltrexone, humans, monkeys, dogs, guinea pigs, rats, and mice □ Antagonists, narcotic—naltrexone, pharmacokinetics, humans, monkeys, dogs, guinea pigs, rats, and mice

Naltrexone, a narcotic antagonist, has been suggested for use in the treatment of heroin dependence (1). Since narcotic antagonists provide no stimulus to the patient to return for frequent dosing (2), the availability of a sustained-release drug delivery system is desirable. Such potential delivery systems for naltrexone have been prepared and tested (3, 4).

It is well known that binding to plasma proteins can influence significantly the distribution of a drug, its pharmacokinetic profile, and its duration of phar-