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Controlled Release of Butamben (Butyl *p*-aminobenzoate) through Silicone Membrane by Means of Complexation and Micellar Solubilization[1]

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Permeation of butamben through a silicone membrane was investigated for up to 120 hours in the presence of three complexing agents. The complexes formed between these agents and the drug, each having different stability constants, were considered to serve as reservoirs of the drug. Release-sustaining behavior was evaluated for the three cases in permeation experiments. The rank order of the sustaining power was in agreement with the order of stability of each complex. By employing an agent which forms a stable complex, much drug can be introduced to the solution system. A desired release profile of drug can therefore be achieved by proper choice of a complexing agent. Surfactant micelles are also expected to function as reservoirs of the drug. Among the three surfactants examined, dodecyltrimethylammonium chloride solubilized butamben to a significant extent and showed excellent sustained-release of the drug. Possible application of surfactants to sustained-release systems was indicated.

Keywords——butyl *p*-aminobenzoate; cyclodextrins; 7-(2-hydroxyethyl)theophylline; surfactants; silicone membrane; permeation; sustained-release; drug complexes; micelles; diffusion cell

A possible use of complexation was introduced previously[3,4] as a means of controlling drug release through a synthetic membrane. The prolongation of drug release was observed in the systems containing complexes. This was attributed to the reduced permeation tendency of the complexes formed between a drug and some agents and thereby such complexes may act as reservoirs of drugs. It was suggested 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, some long-term permeation experiments were conducted using three complexing agents which form soluble complexes with different stability constants. In addition to α- and β-cyclodextrins, a xanthine derivative with negligible permeability through a silicone membrane was employed as a complexing agent.

Surfactants were also examined for their possible role in sustaining drug release. Surfactants in aqueous solution are known, above their critical concentrations, to form micelles into

1) Controlled Drug Permeation, Part III. Part II: K. Juni, M. Nakano, and T. Arita, *Chem. Pharm. Bull.* (Tokyo), **25**, 1098 (1977).
2) Location: *Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan.*
3) M. Nakano and N.K. Patel, *J. Pharm. Sci.*, **59**, 77 (1970).
4) M. Nakano, K. Juni, and T. Arita, *J. Pharm. Sci.*, **65**, 709 (1976).

which the drug can partition. 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. 1). Three types of surfactants: anionic, cationic and nonionic surfactants, were investigated as to their solubilizing and release-sustaining behavior toward butamben.

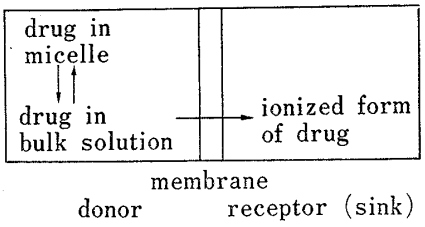

Fig. 1. Schematic Representation of Possible Mechanism of Prolonged Drug Release in the Presence of Micelles

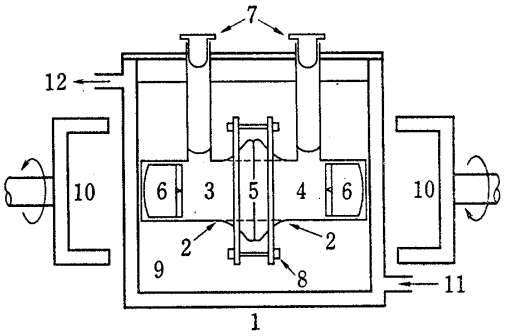

Fig. 2. Illustration of the Apparatus Used in the Permeation Studies

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.

Experimental

Materials and Methods——A medical grade dimethylpolysiloxane sheeting (Silastic nonreinforced, lot HH1355, Dow Corning, Midland, Michigan) in a labeled thickness of 0.01 inches (0.254 mm) was used as a membrane. The following chemicals were used as received: butamben (butyl *p*-aminobenzoate), reagent grade, mp 56.5° and 7-(2-hydroxyethyl)theophylline, reagent grade, mp 158° (both from Tokyo Kasei Kogyo Co., Tokyo); α-cyclodextrin (Corn Products Co., Englewood Cliffs, N.J.); β-cyclodextrin (Teijin Co., Hachioji, Tokyo); polysorbate 80 and sodium lauryl sulfate (both from Wako Pure Chemical Industries, Ltd., Osaka); dodecyltrimethylammonium chloride (Tokyo Kasei Kogyo Co., Tokyo).

The diffusion cell used in the present experiments is shown in Fig. 2. The glass cell consisted of the donor and receptor compartments (22 mm in internal diameter and length of one compartment 40 mm), 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 the circulating water from the constant temperature bath (Model FS, Haake, Berlin). 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. In this experiment, the rotating speed was kept at around 500 rpm. Ten milliliters of solution occupied each compartment.

Preparation of test solutions and the analytical methods were similar to those reported previously.[4] 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 ultraviolet (UV) determination and the same volume of the hydrochloric acid solution was added to the receptor compartment to replace the reduced volume.

In the permeation profiles (Fig. 4, 6, and 7), cumulative amounts of the drug permeated, expressed in terms of concentration, are plotted against time.

The solubilities of butamben in solutions of 7-(2-hydroxyethyl)theophylline were measured by means of dual-wavelength UV spectrophotometry (Model 556, Hitachi Manufacturing Co., Tokyo) at the following two wavelengths, λ_1=258 nm and λ_2=285 nm.

Results and Discussion

Long-term Release Studies of Xanthine and Cyclodextrin Complexes

In Fig. 3, the solubilities of butamben in solutions of three complexing agents are presented. The solubility of the drug increased linearly with the concentration of α-cyclodextrin, whereas β-cyclodextrin formed a complex with a limited solubility. In the 7-(2-hydroxyeth-

yl)theophylline (HET) system, the solubility diagram was somewhat curved upward. This can be due either to formation of a higher-order complex or to an artifact caused by assay procedures.

With the assumption that these complexes are of the 1:1 type, stability constants of butamben complexes were calculated[5] to be $2.2\times10^{3}\,\mathrm{M}^{-1}$, $5.4\times10^{2}\,\mathrm{M}^{-1}$ and $32\,\mathrm{M}^{-1}$ for β-cyclodextrin, α-cyclodextrin and HET, respectively.

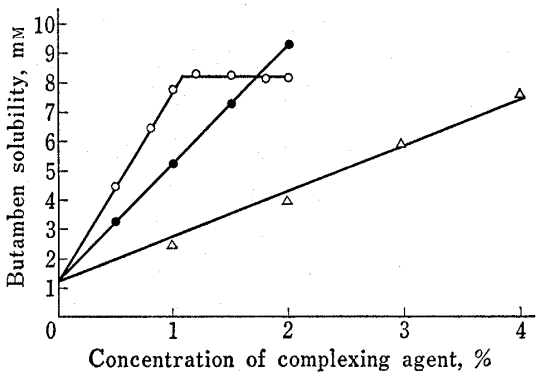

Fig. 3. Solubility Profiles of Butamben in Solutions of Three Complexing Agents at 30°

○, β-cyclodextrin; ●, α-cyclodextrin; and △, 7-(2-hydroxyethyl)theophylline.

Long-term permeation studies were carried out for these systems (Fig. 4). Solubilities of butamben in solutions of 1% β-cyclodextrin, 1.6% α-cyclodextrin and 4% HET were all about 7.7 mM (Fig. 3). Of these complexing agents used, cyclodextrin are assumed not to permeate through the membrane to a detectable extent due to their negligible lipophilicity. HET, on the other hand, does permeate but only slightly due to its poor lipophilicity. Preliminary experiments showed that permeation of HET can be ignored compared to that of butamben. Since the total amounts of the drug originally contained in the donor solutions were almost the same in the three cases, the permeation profiles of three systems should have a common plateau at infinite time.

When a simple saturated solution was used, 95% of the total drug originally contained in the donor solution was released in 8 hours (Fig. 4, Inset). For the HET system, the drug was released almost completely within 60 hours. For α- and β-cyclodextrin systems, the release continued even after 120 hours.

For such systems as the present ones (*i.e.* when the permeability of the complexing agent is negligible and the saturated solution containing the same amount of drug is used),

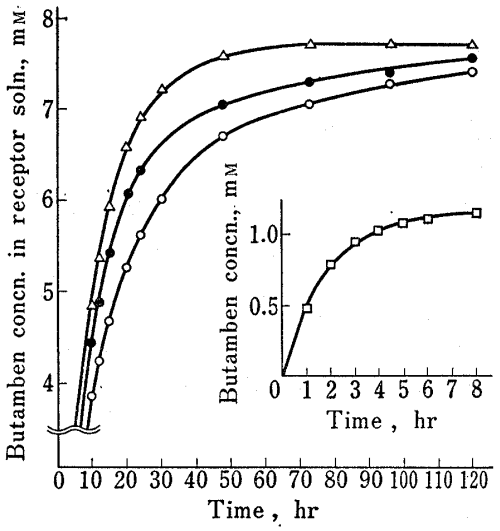

Fig. 4. Long-term Release Profiles of Butamben from Saturated Solutions at 30°

○, 1% β-cyclodextrin; ●, 1.6% α-cyclodextrin; and △, 4% 7-(2-hydroxyethyl)theophylline. Inset: □, simple saturated solution in water.

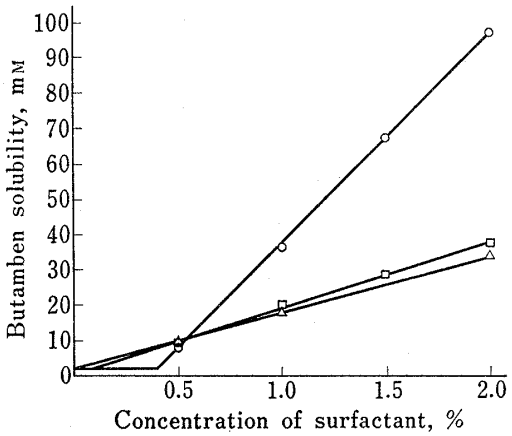

Fig. 5. Solubility Profiles of Butamben in Solutions of Three Surfactants at 30°

○, dodecyltrimethylammonium chloride; △, polysorbate 80; and □, sodium lauryl sulfate.

5) T. Higuchi and K.A. Connors, *Advan. Anal. Chem. Instr.*, **4**, 117 (1965).

it may be generalized that the more stable the complex is, the longer is the duration of drug release through the membrane because the more stable the complex is, the smaller is the fraction of a free drug available for permeation.

Release Studies of Systems Containing Micelles

Solubility diagrams of butamben in the presence of three types of surfactants are shown in Fig. 5. 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 (DTAC), a cationic surfactant, had a relatively high cmc (about 0.4%) and solubilized butamben to a significant extent at higher concentrations. Solubility of butamben in 2% DTAC solution was about 80 times that in water. Sodium lauryl sulfate and polysorbate 80 also solubilized butamben but to a smaller extent.

In Fig. 6 are shown short-term release profiles of butamben from its saturated solutions in 2% solutions of the surfactants. Up to 8 hours, a nearly constant release rate was obtained in the three cases. DTAC exhibited excellent ability to maintain constant release of the drug which was very close to that from the suspension. This corresponds to its greater solubilizing ability shown in the solubility profiles. Therefore, a surfactant which, above its cmc, can solubilize the drug to a greater extent seems to have a larger release-sustaining power. Mechanism involved in sustaining drug release in the presence of a surfactant may be considered similar to those reported previously for complexes[4] and is illustrated in Fig. 1. Micelles also are expected 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.

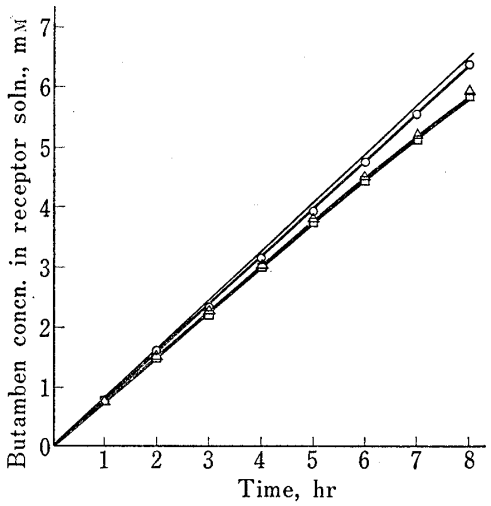

Fig. 6. Release Profiles of Butamben from Saturated Solutions in 2% Surfactant Solutions at 30°

○, dodecyltrimethylammonium chloride; △, polysorbate 80; and □, sodium lauryl sulfate. ——: aqueous suspension.

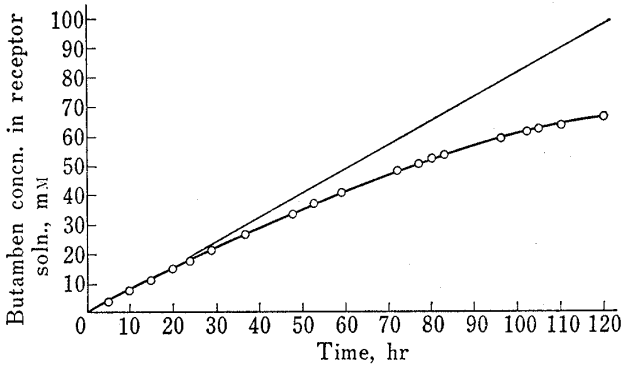

Fig. 7. Long-term Release Profile of Butamben from Its Saturated Solution in 2% Dodecyltrimethylammonium Chloride Solution at 30°

○, surfactant solution; ——, aqueous suspension, see text.

In Fig. 7 is illustrated a long-term release profile of butamben from its saturated solution in 2% DTAC solution. For comparison, the release profile from butamben suspension, which was extrapolated from the short-term study up to 8 hours, is also shown. In the cyclodextrin and HET systems, rapid decrease in release rate was observed after 1 day. In the DTAC system, on the other hand, 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 serve as a reservoir.

It is concluded from these results that some agents which form soluble complexes with the drug can be used to sustain release of the drug through a synthetic membrane. It is known that constant release of a drug (zero-order release) is obtained when a suspension is used as a reservoir[6] and the amount of the drug released is proportional to square root of time when the drug is dispersed in a matrix.[7] In this experiment, it has been demonstrated that nearly constant and sustained release of the drug can be obtained for a limited period even when the drug solution is used. The stability constant of a drug complex can be conveniently employed to predict the release rate of drug and the duration of release when a complexing agent is to be selected. Greater release rate and longer duration of release can be achieved by a proper selection of surfactants. As mentioned earlier, surfactant solutions can retain drugs in solution to a great extent due to micellar solubilization. It can thus serve as a large reservoir of the drug.

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6) R.W. Baker and H.K. Lonsdale, in "Controlled Release of Biologically Active Agents," A.C. Tanquary and R.E. Lacey, Eds., Plenum Press, New York, N.Y., 1974, pp. 25—30.
7) T. Higuchi, *J. Pharm. Sci.*, **50**, 874 (1961).