[Chem. Pharm. Bull. 25(5)1098—1100(1977)]

UDC 615.453.033 : 547.583.5.09

Controlled Drug Permeation. II.[1] Comparative Permeability and Stability of Butamben and Benzocaine

KAZUHIKO JUNI, MASAHIRO NAKANO, and TAKAICHI ARITA

Faculty of Pharmaceutical Sciences, Hokkaido University[2]

(Received July 19, 1976)

Local anesthetic agents, benzocaine and butamben were compared for their permeabilities to silicone membrane and stabilities against hydrolytic degradations in 0.05N NaOH solutions. Butamben permeated through the membrane from the suspension to the same extent as benzocaine in spite of smaller solubility in water. Calculated stability of butamben in suspension was about 10 times greater than benzocaine due to smaller hydrolytic rate constant and smaller solubility. These properties of butamben may be favorable for the delivery system using a silicone membrane as a release-controlling barrier.

Keywords——controlled drug release; silicone membrane; permeability; stability; local anesthetics; benzocaine; butyl *p*-aminobenzoate

When therapeutic agents are released from a drug delivery system for an extended period of time, these agents are usually in liquid, suspension or solution within a reservoir.[3] When selecting a suitable agent for the delivery system among the homologs, both permeability and stability have to be considered as well as pharmacological properties. As to the steady-state flux from saturated solutions of *p*-aminobenzoate esters, Flynn and Yalkowsky[4] examined the effect of carbon numbers of alkyl chain on solubility and flux.

In the present study, both permeability and stability of butamben and benzocaine are examined and some considerations to be taken into when selecting a suitable agent for membrane-controlled release are discussed.

Experimental

Materials——The medical grade dimethylpolysiloxane sheeting (Silastic non-reinforced, lot HH0842, Dow Corning, Midland, Mich.) in a labeled thickness of 5 mil. (0.127 mm) was used as a release-controlling membrane. Benzocaine, Japanese Pharmacopeial grade and butyl *p*-aminobenzoate (butamben), reagent grade were purchased from Torii Pharmaceuticals, Tokyo and Tokyo Kasei Kogyo Co., Tokyo, respectively. They were checked for purity by differential scanning colorimeter and were used without further purification.

Permeation Studies——Suspensions used in permeation studies were prepared in a water-jacketed-beaker maintained at 30° by stirring an excess amount of the drug in water for 2 days. Sampling and analytical procedures as well as the diffusion cell used were described previously.[1] The contents of both compartments of the cell were stirred with electric motor-driven propellers.

Stability 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 Shimadzu Model UV-300 double-beam/difference/dual-wavelength 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.

1) Part I: M. Nakano, K. Juni, and T. Arita, *J. Pharm. Sci.*, **65**, 709 (1976).
2) Location: *Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan.*
3) F.E. Yates, H. Benson, R. Buckles, J. Urquhart, and A. Zaffaroni, in "Advances in Biomedical Engineering," Vol. 5, J.H.U. Brown and J.F. Dickson, Eds., Academic Press, New York, N.Y., 1975, pp. 1—34.
4) G.L. Flynn and S.H. Yalkowsky, *J. Pharm. Sci.*, **61**, 838 (1972).

Results and Discussion

Permeation Studies

When a suspension is applied in the donor side, release rate of the drug through the membrane dM/dt is given by

$$\frac{dM}{dt} = \frac{PAC_s}{l} \quad (1)$$

where P=permeability defined as a product of diffusivity in the membrane D and distribution coefficient between the membrane and the donor solution K_d ($P=DK_d$), A=surface area of the membrane, C_s=solubility of the drug in the donor solution, and l=thickness of the membrane. At constant temperature and pH, since P and C_s are constant, the release rate is expected to be constant.

Release profiles of benzocaine and butamben through silicone membrane from their suspensions are shown in Fig. 1. Constant release rate (zero-order release) was observed in each case. Furthermore, their release profiles were nearly superimposed. The release rates for benzocaine and butamben estimated from the slopes were 6.48×10^{-9} and 6.36×10^{-9} moles/sec, respectively, indicating that moles of anesthetics permeating through the membrane per unit time were almost equal in spite of a large difference in their respective solubilities in aqueous solution. Namely, since

$$\left(\frac{dM}{dt}\right)_{benz} \simeq \left(\frac{dM}{dt}\right)_{but}$$

and A(7.79 cm^2) and l (127 μm) are identical in both experiments, it follows from Eq. 1 that

$$(PC_s)_{benz} \simeq (PC_s)_{but}$$

On the other hand, since

$$(C_s)_{benz} = 7.5 \text{ mM} > (C_s)_{but} = 1.2 \text{ mM}$$

at 30°, there must be difference in permeability.

$$P_{benz} < P_{but}$$

The permeabilities of benzocaine and butamben were calculated to be 1.4×10^{-6} and 8.6×10^{-6} cm^2/sec, respectively.

Since the difference in molecular size, which determines the diffusivity D in the membrane,[5] is not very much between the two, higher permeability of butamben arises primarily from its larger distribution coefficient K_d.[4]

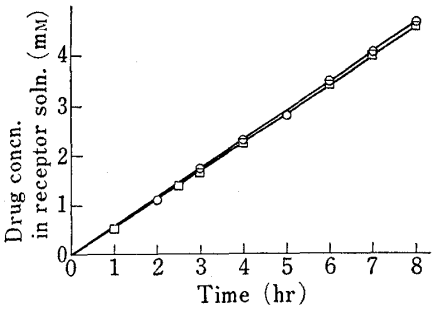

Fig. 1. Permeation Behaviors of Benzocaine (○) and Butamben (□) through a Silicone Membrane from Suspensions at 30°

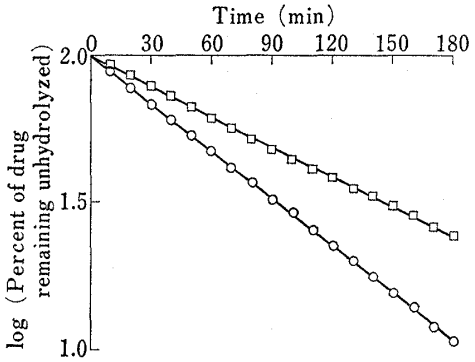

Fig. 2. Rates of Hydrolysis of Benzocaine (○) and Butamben (□) Solutions in 0.05 N NaOH at 30°

5) 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, p. 20.

Stability Studies

As shown in Fig. 2, semi-logarithmic plots of the concentrations of unhydrolyzed benzocaine and butamben *vs.* time gave linear profiles (pseudo-first-order reaction). The rate constant k and the half-life $t_{1/2}$ for the reaction were determined from the slope and are listed in Table I. Benzocaine was found to be hydrolyzed more rapidly than butamben, indicating that butamben is more stable against hydrolysis in alkaline solution than benzocaine. Similar observation has been reported recently by Smith, *et al.*[6]

In suspension, concentration of the drug in solution is kept constant at its solubility C_s, the rate of hydrolysis $-dC/dt$ can then be written by

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

where k=first-order rate constant. Since both k and C_s 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 I. 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 I. Solubilities and Rate Constants of Hydrolysis at 30°

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

General Discussion

From permeation and stability studies, it has been shown that butamben permeates through the membrane from its suspension as fast as benzocaine in spite of lower solubility in water and that butamben is about 10 times as stable as benzocaine against hydrolysis. Thus it may be suggested that butamben is preferable to benzocaine when used in the delivery system employing a partition membrane as a release-controlling barrier. It can be generally stated that in such delivery system, examinations of a drug for its permeability to the membrane and stability in the reservoir give a meaningful suggestion to proper choice of a drug from a series of homologs.

Acknowledgement A part of this study was supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture which is gratefully acknowledged.

6) G.G. Smith, D.R. Kennedy, and J.G. Hairn, *J. Pharm. Sci.*, **63**, 712 (1974).