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Diffusion kinetics of alkyl *p*-aminobenzoates in silicone polymers and their release from silicone reservoir devices

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Summary

The permeation of alkyl *p*-aminobenzoates through silicone membranes and their in vitro release from silicone reservoir devices were studied. The permeability of ethyl *p*-aminobenzoate was practically the same among the different silicone polymers tested. Steady-state flux was maximal with ethyl, propyl and butyl esters of *p*-aminobenzoic acid. It appears that the diffusion and partitioning properties were optimal with these esters. On the basis of the activation energies of permeation, the flux of hexyl ester may be limited by the aqueous diffusion layer, while permeation of the other esters is controlled by membrane partitioning and diffusion. Without osmotic additives the release of *p*-aminobenzoic acid and its potassium salt from the silicone reservoir devices was negligible. Alkyl *p*-aminobenzoates were released from the devices at a nearly constant rate for 22 h. The osmotic flux of water accelerated the release of all the model drugs tested. The relative accelerating effect of osmotic additives was increased with increasing hydrophilicity of the model drugs.

Introduction

Silicone elastomers are widely used as rate-controlling membranes or matrix polymers in controlled release dosage forms (Chien, 1976; Hsieh et al., 1985; Rankin and Aguadisch, 1987). This is due to their inertness, biocompatibility and high permeability to several drugs. Hydrophobic silicone polymers can be used to control the release of lipophilic and relatively non-polar drugs, that are able to partition in silicone polymers. Polar drugs can be delivered from silicone matrices only when hydrophilic additives are dispersed in silicone (McGinity et al., 1979; DiColo et al., 1982). In this case drug release is triggered by osmotic imbibition of water in the matrix. Nevertheless, drug release is often unpredictable and release rate is not constant (DiColo et al., 1982; Hsieh et al., 1985; DiColo et al., 1986).

In this study, we determined the permeation of five alkyl *p*-aminobenzoates through silicone membranes and their release rates from silicone reservoir devices. Our aim was to evaluate the diffusion kinetics of alkyl *p*-aminobenzoates in silicone membranes and the effect of the osmotic additive in the device core on the release rate of the model drugs.

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Materials and Methods

Materials

Silastic 382, MDX 4-4210 and Q7-4840 A/B medical grade silicone elastomers (Dow Corning, Midland, MI) were base materials used for silicone membranes. *p*-Aminobenzoic acid (PABA), its potassium salt (K-PABA) and methyl, ethyl, *n*-propyl and *n*-butyl esters were from Sigma (St. Louis, MO) and *n*-hexyl *p*-aminobenzoate was synthesized using a literature procedure (Flynn and Yalkowsky, 1972). NaCl and NaH_2PO_4 were used as osmotic additives in the devices. Model drugs were sieved and a particle size fraction of 88–149 μm was used in the studies.

Preparation of membranes and silicone reservoir devices

For preparing Silastic 382 membranes, 0.5% (w/w) of curing agent (Catalyst M; Dow Corning) was mixed carefully with the elastomer. Membranes were prepared by compressing the mixture with a hydraulic press (model C laboratory press, Carver, Menomonee Falls, WI) at room temperature for 30 min. MDX 4-4210 membranes were prepared by mixing 10% (w/w) of MDX-4240 curing agent with elastomer. The membranes were moulded in the hydraulic press at 60 °C for 1 h. To prepare Q7-4840 membranes, components A and B were mixed in equal portions. The mixture was cured in the hydraulic press for 1 h at 60 °C. The pressure used in compressing the polymer membranes was 0.94 MPa in all cases. The thickness of resulting membranes was about 600 μm. For permeation studies circular discs (diameter 15 mm) were cut from the membranes. Smaller pieces (about 5 × 5 mm) were cut for determination of partition coefficients.

Silicone reservoir devices were made of Q7-4840 membranes. Samples of model drugs with or without osmotic additives were placed on a silicone disc. For the devices with PABA and K-PABA the amount of the model drug and osmotic additive was 5 mg, the thickness of the disc being 150 μm. For the devices containing alkyl *p*-aminobenzoates, 10 mg of esters and NaCl were used and a disc thickness of 600 μm. The upper silicone membrane was glued onto the lower membrane with Silastic™ adhesive type B (Dow Corning, Valbonne, France) leaving the model drug and possible additive encapsulated between the membranes.

Solubility and distribution coefficient of alkyl p-aminobenzoates

For determining the aqueous solubility of PABA, K-PABA and alkyl *p*-aminobenzoates, a suspension of each drug was made in phosphate buffer (0.1 M, pH 7.4). The suspension flasks were shaken for 6–8 days at 34 °C. Thereafter, samples were withdrawn and filtered, and the concentration of alkyl *p*-aminobenzoate in the sample was determined using a UV spectrophotometer at 284 nm, except for the hexyl ester, which was evaluated at 282 nm and PABA and K-PABA at 264 nm.

For determining the distribution coefficients of the esters between the silicone membrane and phosphate buffer, 2 g of small pieces of each silicone membrane were placed in an injection vial with 5 ml of alkyl *p*-aminobenzoate solution (concentration about 50% of saturation solubility). The vials were closed tightly to minimize evaporation. Polymer was equilibrated with the ester solution at 34 °C for 2 weeks. The equilibrium drug concentration in silicone polymers was obtained from the depletion of alkyl *p*-aminobenzoate from solution. The distribution coefficient, K, was calculated using Eqn. 1:

$$K = \frac{V_s(C_0 - C_s)}{V_m C_s} \quad (1)$$

where V_s is the volume of solution, V_m is the volume of the membrane, C_0 is the initial drug concentration in solution and C_s is the drug concentration in solution at equilibrium.

The concentration of alkyl *p*-aminobenzoate in the samples was analysed spectrophotometrically at 284 nm, except for hexyl ester, which was determined by HPLC. HPLC analyses were performed using a reverse-phase C18 column (5 μm, 8.0 × 0.4 cm) (Zorbax ODS; DuPont, Wilmington, DE). Detection wavelength was 282 nm, and retention time was 5 min when a mobile phase of acetonitrile/water (1 : 1, v/v) was used at a flow

rate of 1.0 ml/min. Each experiment was repeated three times.

Polymer solubility of alkyl *p*-aminobenzoates was calculated by multiplying the aqueous solubility by the distribution coefficient of the esters.

Permeation measurements

Permeation of alkyl *p*-aminobenzoates through silicone membranes was determined by using a modified Touitou diffusion cell (Touitou and Abed, 1985). The volume of both compartments in the diffusion cell was 15 ml. The effective surface area of the membrane in contact with the solution was 1.77 cm^2.

The membrane was mounted carefully between the compartments. The donor compartment was filled with a saturated suspension of the *p*-aminobenzoate ester in buffer solution. The receiving solution was blank phosphate buffer (pH 7.4, 0.1 M). During the experiment the diffusion cells were shaken at 160 rpm. Saturated suspensions of the *p*-aminobenzoate esters were used in order to maintain a constant thermodynamic activity in the donor phase and to provide maximal solute fluxes.

At 2-h intervals the receptor phase was completely changed to fresh phosphate buffer in order to maintain sink conditions. Concentrations of the esters in the samples were analysed as described above. Six membranes were tested in each case.

Release of model drugs from silicone reservoir devices

In vitro release of PABA and K-PABA from silicone devices in phosphate buffer (pH 7.4) was determined at 34°C using side-bi-side diffusion cells (DC-100B, Crown Glass, Somerville, NJ) and release of methyl, ethyl, propyl and butyl esters using stoppered flasks. The volume of each compartment in the diffusion cell was 3.4 ml and the surface area of the device in contact with the receiving phase was 0.64 cm^2. Samples were withdrawn or receptor phase was completely changed to fresh phosphate buffer at fixed times in order to maintain sink conditions. The concentrations of alkyl esters of PABA in the samples were analyzed spectrophotometrically at 284 nm. PABA and K-PABA were determined at 264 nm using HPLC and the column described above. The mobile phase was 5% (v/v) of acetonitrile in phosphoric acid (pH 2.1) and retention time 1.5 min at a flow rate of 1.0 ml/min. Six devices were tested in each case.

Analysis of data

Normalised flux ($J_{ss}l$; μg/h per cm) and permeability coefficient (P; cm^2/s) for solute permeation in silicones were calculated according to Eqn. 2 (Baker and Lonsdale, 1974):

$$J_{ss} = \frac{P\Delta C}{l} = \frac{DK\Delta C}{l} \tag{2}$$

where J_{ss} is the steady-state flux across the membrane (i.e. the slope of the cumulative amount permeated vs. time plot at steady state), ΔC is the concentration difference across the membrane, l is the thickness of the membrane, D is the diffusion coefficient of the permeant in the membrane and K is the distribution coefficient of the permeant between the membrane and buffer solution. The diffusion coefficient was not determined since all tested silicone polymers contain silica filler, which may interfere with permeant diffusion in polymer and make determination of diffusion coefficient very unreliable (Most, 1970).

Flux of alkyl esters of PABA through MDX 4-4210 membranes was determined at 5, 23 and 34°C as described above. Activation energy of flux was determined using the Arrhenius relationship (Ghannam et al., 1986):

$$\log J_{ss}l = \text{constant} - \frac{\Delta E_a}{2.303R} \cdot \frac{1}{T} \tag{3}$$

where ΔE_a is the activation energy of permeation, R is the gas constant and T is the absolute temperature. The activation energy of permeation (ΔE_a) is the sum of the activation energies of diffusion (E_h) and solvation in polymer (ΔH_{TS}).

The apparent release rate of the model drugs from the devices was determined as the slope of the linear portion of the drug released vs. time plot. The release rates were normalised by the membrane thickness and surface area of permea-

tion. The statistical significance of the differences was tested using Mann-Whitney's U-test.

Results and Discussion

The variation in solubility of alkyl *p*-aminobenzoates in silicone polymers was 3-fold and in phosphate buffer (pH 7.4) more than 100-fold (Table 1). Polymer solubility increased with chain length from the methyl to butyl ester (Table 1). The hexyl ester, however, had lower solubility in polymer than the butyl ester. The relationship between aqueous solubility and alkyl chain length of the *p*-aminobenzoate esters was semilogarithmic.

The logarithm of the polymer-buffer solution distribution coefficient (K) was linearly dependent on the alkyl chain length of the PABA esters (Fig. 1). The slope of the plot of log K vs. alkyl ester chain length was 0.503. For most nonpolar solvents this slope, commonly designated π, is usually about 0.5 (Yalkowsky et al., 1972). In our study the distribution coefficient increased 3.2-fold per methylene unit.

Steady-state flux of alkyl *p*-aminobenzoates in silicones was maximal with ethyl, propyl and butyl ester, of PABA (Fig. 2). On increasing the lipophilicity of alkyl *p*-aminobenzoates, their partitioning in silicone polymer was improved but the decelerated diffusion due to the increase in molecular weight of the PABA esters compensates this increase. The net result is that the flux of ethyl, propyl and butyl esters across the silicone membrane remained practically the same. Although hexyl *p*-aminobenzoate is more lipophilic than the other esters studied, its flux through the hydrophobic silicone membrane was the lowest. This may be due to the low value of the diffusion coefficient for the large hexyl ester in silicone polymer.

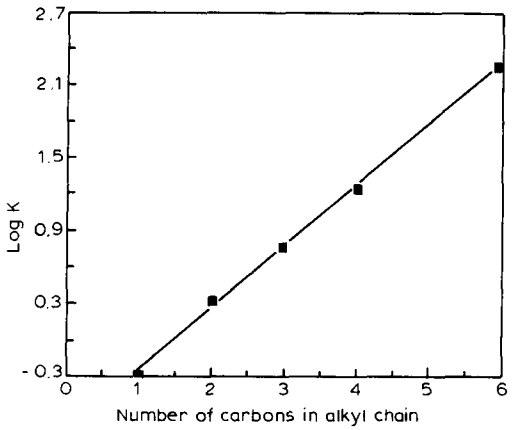

Fig. 1. Silicone membrane-phosphate buffer distribution coefficients (K) of alkyl *p*-aminobenzoates at 34 °C (log $y = 0.503x + 0.740$; $r = 0.9994$, $n = 3$).

The steady-state flux values of ethyl *p*-aminobenzoate in Silastic 382, MDX 4-4210 and Q7-4840 polymers at 34 °C were $2.6 \pm 0.04 \times 10^{-6}$, $2.4 \pm 0.09 \times 10^{-6}$ and $2.3 \pm 0.04 \times 10^{-6}$ mg/cm per s (means ± SE), respectively. Thus, the flux of ethyl ester of PABA through the silicones was almost equal among the tested silicones.

TABLE 1

Molecular weights, silicone polymer-buffer distribution coefficients (K) and solubilities of alkyl p-aminobenzoates in phosphate buffer (pH 7.4) (C_s) and in silicone elastomer (C_p) at 34 °C

Means ± SE of three determinations are presented.

Ester	Molecular weight	K	C_s (mg/ml)	C_p [a] (mg/ml)
Methyl	151	0.53 ± 0.11	2.52 ± 0.04	1.33 ± 0.28
Ethyl	165	2.09 ± 0.04	1.50 ± 0.06	3.14 ± 0.13
Propyl	179	5.74 ± 0.05	0.67 ± 0.01	3.85 ± 0.04
Butyl	193	19.03 ± 0.39	0.21 ± 0.01	4.00 ± 0.13
Hexyl	221	185.19 ± 1.36	0.02 ± 0.01	3.74 ± 0.22

[a] $C_p = C_s K$.

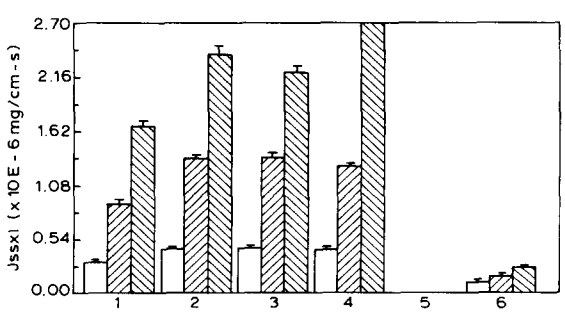

Fig. 2. Normalised steady-state fluxes of alkyl *p*-aminobenzoates, $J_{ss}l$, through silicone membranes at 5 °C (□), 23 °C (▨) and 34 °C (▩). Means ± SE of six determinations are presented.

TABLE 2

Normalised release rates of p-aminobenzoic acid (PABA), its potassium salt (K-PABA) and methyl, ethyl, propyl and butyl esters from silicone reservoir devices at 34 °C

Means ± SE of six determinations are presented. n.d., not detectable.

Model drug	Release rate (μg/h per cm)
PABA	$1.9\times10^{-2}\pm0.3\times10^{-2}$
PABA + NaCl	$3.3\times10^{-2}\pm0.2\times10^{-2}$
K-PABA	n.d.
K-PABA + NaCl	n.d.
K-PABA + NaH_2PO_4	$6.2\times10^{-2}\pm0.8\times10^{-2}$
Methyl ester	2.4 ± 0.2
Ethyl ester	4.2 ± 0.1
Propyl ester	4.4 ± 0.2
Butyl ester	4.2 ± 0.2

The rate of permeation increased 2–6-fold with rise in temperature from 5 to 34 °C (Fig. 2). The activation energy for permeation of hexyl *p*-aminobenzoate in MDX 4-4210 polymer was 4.9 ± 0.4 kcal/mol. For methyl, ethyl, propyl and butyl esters the respective activation energies were 9.6 ± 0.2, 9.8 ± 0.2, 9.4 ± 0.1 and 10.5 ± 0.4 kcal/mol. Diffusion in aqueous media requires a low energy of activation (about 5 kcal/mol) (Grass and Robinson, 1988), whereas partitioning in lipophilic membranes requires higher values (Grass and Robinson, 1988). On the basis of the activation energies, diffusion of the hexyl ester in the aqueous diffusion layer of the donor compartment may be the rate-determining step in its permeation. Partitioning in the polymer appears to be the most important step in permeation of the other esters.

The release of PABA from silicone reservoir devices was very slow (Table 2). NaCl increased the release rate of PABA 1.7-fold. Almost completely ionized K-PABA was unable to permeate the silicone membrane. NaCl did not affect the release of K-PABA, however, when NaH_2PO_4 was encapsulated with K-PABA between the silicone membranes, about 10% of K-PABA was released over a period of 1 week. NaH_2PO_4 probably imbibed water in the device and decreased the pH of the resulting solution inside it. Consequently, the degree of drug ionization in the core was

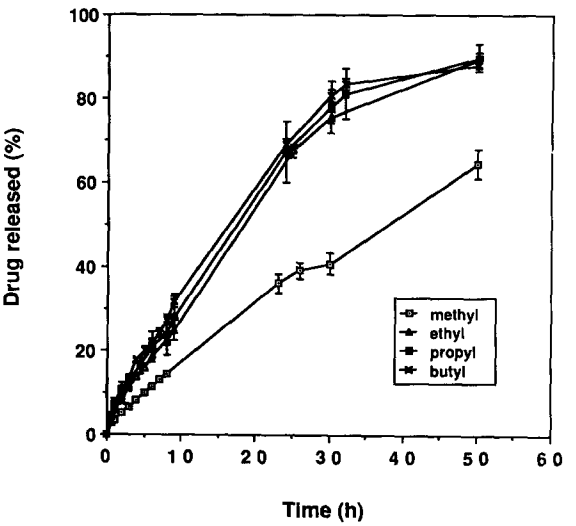

Fig. 3. Release of methyl, ethyl, propyl and butyl *p*-aminobenzoates from silicone reservoir devices at 34 °C. Means ± SE of six determinations are presented.

decreased, partitioning of PABA in silicone increased, and its release accelerated.

After an initial burst (< 4 h), alkyl *p*-aminobenzoates were released from the silicone reservoir devices at a nearly constant rate for 22 h (Fig. 3). The effect of NaCl on the release of alkyl esters of PABA was heightened with increasing hydrophilicity of the esters (Fig. 4). The release of methyl *p*-aminobenzoate was accelerated significantly ($p < 0.05$), while that of the lipophilic pro-

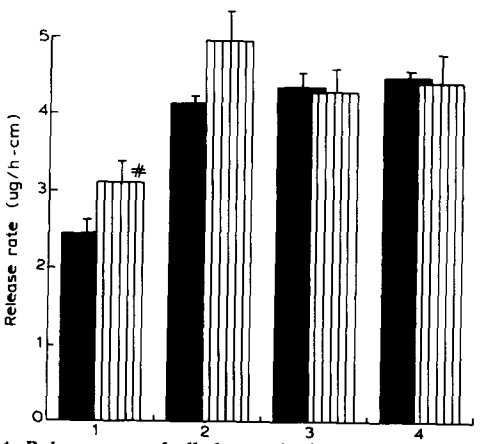

Fig. 4. Release rate of alkyl *p*-aminobenzoates from silicone reservoir devices with (▥) and without (■) NaCl. Means ± S.E.; $n = 6$. # $p < 0.05$.

pyl and butyl esters, that partitioned well in silicone, was not affected by NaCl.

In conclusion, the reservoir device, in which the drug is encapsulated between two silicone membranes, constitutes a simple system for achieving zero-order drug release. Osmotic additives in the core of the device accelerated the release of hydrophilic drugs from the silicone reservoir devices. At present, the mechanisms of release remain unclear.

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