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Water-activated and pH-controlled release of weak bases from silicone reservoir devices

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Summary

The release of lipophilic (propranolol) and hydrophilic (sotalol) weak bases from silicone reservoir devices was studied. Solid drugs in the form of their hydrochloride salts were entrapped with osmotic or buffering additives between two silicone membranes. Drug release from the device was activated by flux of water into the core of the device. Without additives in the device core, the release of propranolol and sotalol was negligible. Mannitol, a hydrophilic additive, in the silicone membrane increased the water flow into the devices, but it did not increase significantly the release of model drugs. This suggests that no continuous channels had been formed through the silicone walls. Addition of sodium chloride in the core increased the osmotic flux of water in the devices, however, the pH of the device core and the release of model drugs were unaffected. When Tris, disodium phosphate and/or sodium phosphate were incorporated into the core of the silicone devices, the resulting pH after water flux in the device increased and the rate of propranolol release rose several hundred fold. The pH of the core determined the degree of ionization and partitioning of propranolol in the silicone walls. In this way, the rate of drug release could be adjusted to encompass wide range of values by using buffering agents. An initial burst of drug release was avoided with this design but in some cases an initial lag time with slower release was observed. Sotalol was too hydrophilic even in its unionized state to be released through silicone walls.

Introduction

Silicones are lipophilic and nonporous polymers that can be used as rate-controlling membranes or matrix polymers in therapeutic systems. Due to the hydrophobic nature of silicones, they are relatively impermeable to hydrophilic and ionic compounds (Langer and Folkman, 1978; Touitou and Abed, 1985). Permeability of silicones to more polar molecules has been increased by using polar (e.g. glycerol, PEG) and osmotic additives (e.g. sodium chloride) in the polymer (Carelli and Di Colo, 1983; Hsieh et al., 1985; Hoth and Merkle, 1988). The permeation of ionic compounds through hydrophilic membranes can also be enhanced by lipophilization with ion pair formation (Lee and Kim, 1987) or by converting the impermeable, ionized drug into a more permeable, unionized form with pH-adjusting additives (Ebert et al., 1987).

Constant zero-order release of drugs can be achieved from reservoir devices with a constant drug activity source (e.g. suspension) in the core of

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the device (Baker and Lonsdale, 1974). However, during storage, the drug partitions from the core to saturate the release rate-limiting membranes. Consequently, an initial burst precedes the period of constant drug release. The burst effect was recently avoided with the use of a two-compartment reservoir device, where the drug does not partition to the membrane before the compartments are mixed together by pressuring the device (Ebert et al., 1987).

In this study, the model drugs were the weak bases, propranolol and sotalol. They were entrapped as solid-state salts between two silicone membranes. Our first aim was to evaluate whether water imbibition can trigger drug release from the device. Secondly, we wanted with this design to control the final release rate of the weak bases with the resulting core pH during water influx into the device.

Materials and Methods

Preparation of devices

The membranes for silicone reservoir devices were made of Q7-4840 A/B medical grade silicone elastomer (Dow Corning, Midland, MI). A and B components were mixed in equal portions. The membranes were prepared by compressing the mixture with a hydraulic press (Carver model C laboratory press, Carver, Menomonee Falls, WI) at 60 °C for 1 h at a pressure of 0.94 MPa. D-(−)-Mannitol (Merck, Darmstadt, F.R.G.) was used as a hydrophilic additive in the membranes. Before use mannitol was micronized by sonication (Soniprep 150, MSE Scientific Instruments, Manor Royal, Sussex, U.K.) and its mean particle size was 20 μm. Before vulcanization 20% (w/w) of mannitol was carefully mixed with silicone polymer. During vulcanization, mannitol was entrapped in the polymer and formed separate particles in the silicone material as demonstrated by microscopic examination. Circular discs with a thickness of about 150 μm and diameter of 22 mm were cut from the membranes and further used in the experiments.

Sotalol hydrochloride (Farmos Group, Turku, Finland) and propanolol hydrochloride (Sigma, St. Louis, MO) were used as model drugs in

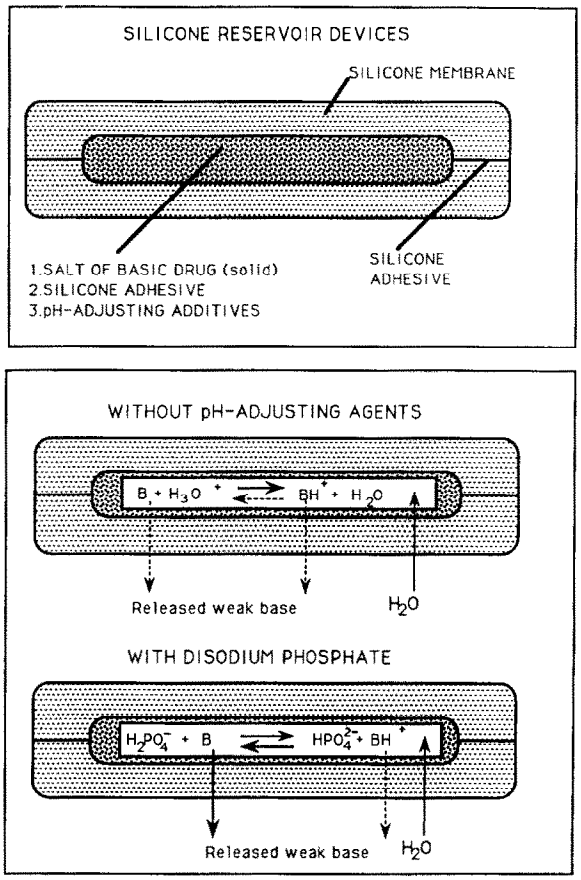

Fig. 1. pH-controlled silicone reservoir devices.

silicone reservoir devices. NaCl (Ph. Eur.), Tris (Sigma), disodium phosphate (Merck), sodium phosphate (BDH Chemicals, Poole, U.K.) and the mixtures of the phosphates were used as additives in the device core. The adjuvants were sieved before use and the particle size fraction of 88–149 μm was used in the studies. When reservoir devices were prepared, samples of model drugs (2 mg) with or without additives (2 mg) were placed on a silicone disc. 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 (Fig. 1).

Permeation measurements

Permeability of water in the membranes was studied in side-by-side diffusion cells (DC-100,

Crown Glass, Somerville, NJ) at 34°C. Silicone membranes with or without mannitol were placed in the diffusion cells. Distilled deionized water (3 ml) with 1.9 μCi of tritiated water (specific activity 18 mCi/g; New England Nuclear, Boston, MA) was placed in the donor compartment. The surface area of the membrane in contact with the receiving phase was 0.64 cm^2. The receiving phase contained 3 ml of pure distilled water. At fixed times, samples of 100 μl were withdrawn, diluted with 400 μl of distilled water and 4.5 ml of ACS (Amersham, Arlington Heights, IL) was added. Radioactivity of the sample was determined by liquid scintillation counting (Rackbeta 1216, Wallac, Turku, Finland). Counting was continued for 480 s or until 12 000 counts had accumulated. The steady-state flux of tritiated water across the membrane was determined from the slope of the cumulative amount permeated vs time plot. The fluxes were normalised by the membrane thickness and the surface area of permeation. Each experiment was repeated six times.

Drug release

Drug release from the devices at 34°C was tested in the side-by-side diffusion cells. The device and a glass plate were placed in the diffusion cell so that only one side of the device was exposed to the dissolution medium (phosphate buffer, 100 mM, pH 7.4, 3 ml). At fixed times, samples were withdrawn and the drug concentrations were determined using HPLC with a Hypersil RP-18 column (3 μm, 50 × 4.6 mm) (Shandon Southern Instruments, Sewicley, PA). In the analysis of propranolol, the mobile phase was a binary mixture of 30% (v/v) of acetonitrile and 70% (v/v) of acetic acid (pH 4.0), the detection wavelength being 254 nm. For sotalol the mobile phase contained 15% of acetonitrile in acetic acid (pH 4.0), and was analyzed at 225 nm. At a flow rate of 1.0 ml/min, the retention times were 2.9 and 3.5 min for propranolol and sotalol, respectively. The apparent release rates of model drugs from the devices were determined as the slope of the released amount vs time plot after the initial lag time. The release rates were normalised by the membrane thickness and surface area. Six devices were tested in each case.

pH and amount of water in the device core

For determining the pH of the device core, a device was glued onto a glass plate so that only one side of the device was in contact with the dissolution medium. The devices with glass plates were immersed in a beaker containing 200 ml of 100 mM phosphate buffer at 34°C. After 24, 48 and 72 h, the pH of the device core was measured with microelectrode (Ross 8163, Orion Research, Boston, MA). Since the pH of the device core was nearly constant between 24 and 72 h, the mean of the pH at the three time points was used to characterize the inner pH of the device. The amount of water absorbed in the devices after 72 h was calculated as the weight difference between the wet and dried devices. Each experiment was repeated three times. The statistical significance of the differences was assessed using Mann-Whitney's U-test.

Results and Discussion

Devices without additives

Without additives in the core of the device propranolol hydrochloride and sotalol hydrochloride were very poorly released across the silicone membranes. The rate of propranolol release was less than 0.004%/h and the released amounts of sotalol were below the detection limit. The amount of water absorbed in the devices was 0.2 and 5 μl in the cases of propranolol and sotalol, respectively. Propranolol is poorly water soluble and consequently the osmotic imbibition of water was negligible in this case. Sotalol is a more water-soluble drug and in this situation the osmotic influx of water into the device core is greater. However, in both cases the pH of the resulting saturated solution of the hydrochloride salts of β-blockers is acidic. The pK_a of propranolol is 9.23, and the pK_a values of sotalol are 8.15 and 9.65, respectively (Schoenwald and Huang, 1983). Consequently, the drugs are predominantly in the ionized form in the device core and due to the highly polar nature of the ionized species, most of the drug could not partition in the silicone wall and the release rate was slow.

Effect of core additives

Addition of sodium chloride in the core of the devices increased the osmotic influx of water into the system (from about 10 to 15 μl) but did not accelerate the release of propranolol and sotalol from the devices. It seems that the accelerated flow of water in the devices does not form permanent aqueous channels in the silicone walls, where hydrophilic compounds could penetrate without partitioning to the polymer. Sodium chloride did not change the pH of the device core and the ionization and partitioning characteristics of the drug were unaltered.

Addition of disodium phosphate in the sotalol devices increased the pH of the device core from 6.0 to 7.6, but the rate of sotalol release was still only 23 ng/h. With Tris the inner pH of the device was 8.6 and the rate of sotalol release 59 ng/h.

The pH of the device core during the experiment and the rate of propranolol release from the devices were significantly affected by compounds in the device core (Figs 2–4). The pH and release rate of propanolol were practically equal when 100 or 95% phosphate in the core was in the dibasic form. When the fraction of monobasic phosphate was increased the core pH and release rate of propranolol were decreased (Figs 2 and 3). With Tris buffer, pH in the device core was highest (> 8) and propranolol was released 740-times faster than in the absence of pH-adjusting additives.

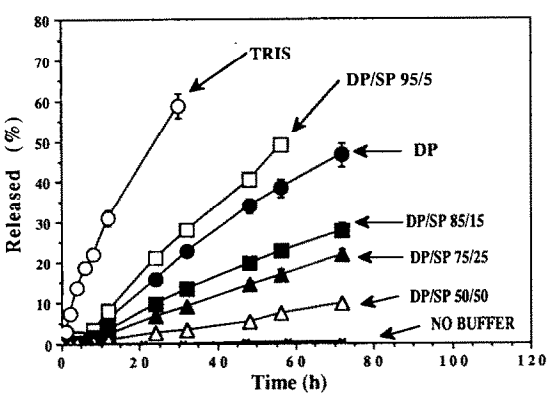

Fig. 2. Release of propranolol (2 mg) from silicone reservoir devices with different pH-adjusting additives (total amount 2 mg) in the core. DP, disodium phosphate; SP, sodium phosphate. Means ± SE of 5–6 experiments are presented.

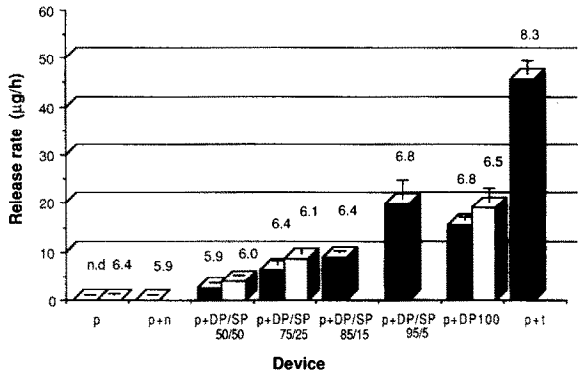

Fig. 3. Effect of mannitol on the release of propranolol (2 mg) from silicone reservoir devices with different pH-adjusting additives (total amount 2 mg) in the core. pH of the core of the corresponding devices is shown above the bars. (Filled bars) Without mannitol; (unfilled bars) with mannitol in the membrane. P, propranolol; N, sodium chloride; DP, disodium phosphate; SP, sodium phosphate; T, Tris. Means ± SE of 3 pH determinations and 5–6 release experiments are shown.

Thus, the rate of drug release can be controlled over a very large range with pH-adjusting agents in the device core. Increased pH decreased the degree of ionization of propranolol, which increases the partitioning of weak bases in the hydrophobic silicone membranes (Urtti et al., 1987). Unionized propranolol is non-polar and penetrates well in silicone. In contrast, due to the polarity of the unionized species of sotalol (Schoenwald and Huang, 1983), this compound could not partition in silicone wall even from solution with elevated pH. Consequently, sotalol was released very slowly in this case as well.

Propranolol release was characterized by an initial lag time (1–5 h) before constant drug release was achieved. The lag time was probably caused by the time elapsed before an adequate amount of water had permeated into the device core to dissolve the drug and additives. Dissolution of the drug salt and additives is a prerequisite for drug release from the system. Zero-order release from reservoir devices is often preceded by faster release of the drug that has partitioned during storage to the rate-limiting membrane of a reservoir device. With the water-activated and pH-controlled device the release burst could be avoided. The amount of water that was absorbed in the device during a period of 72 h was 6–15 μl.

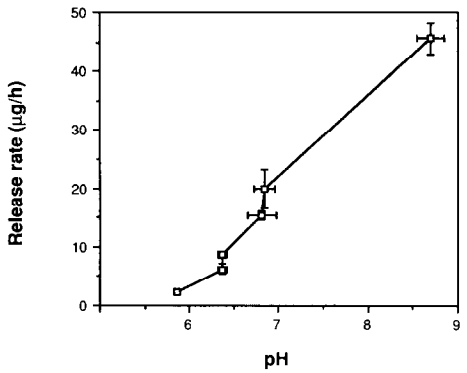

Fig. 4. Effect of the inner pH in the device on the rate of propranolol release from the devices. Means ± SE of 3 pH determinations and 5–6 release experiments are shown.

These data suggest that the delivery system could also function in vivo, when only a small amount of water is available. After the lag time propranolol was released at a constant rate for 48–72 h (Fig. 2).

Effect of mannitol

Mannitol in the silicone membrane accelerated the transport of water across the membranes. In a diffusion cell, ^3H_2O flux across the silicone membrane was $0.5 \pm 0.02 \times 10^{-4}$ $\%h^{-1}$ cm^{-1} without mannitol and $5.5 \pm 0.3 \times 10^{-4}$ $\%h^{-1}$ cm^{-1} with 20% of mannitol in the membrane. Mannitol is a highly water-soluble compound that dissolves when water penetrates into the silicone membrane. At the sites of dissolved mannitol, particle resistance to water transport is decreased and the overall water flux across the membrane is increased. Although mannitol increased water absorption into the devices several fold (from about 10 to 50 μl), the rate of sotalol release was very slow, suggesting that no continuous channels had been formed through the silicone walls. Mannitol rather increases the sotalol flux by forming separate cavities filled with mannitol solution. The thickness of the device wall, however, had a crucial effect on sotalol release from the devices. When the thickness of the silicone wall was about 150 μm the amounts of sotalol released were below the detection limit. For devices with a wall of 100 μm the rate of sotalol release was as high as 1 μg/h. With Tris or disodium phosphate in the device core, the rate of sotalol release was 39 and 28 ng/h, respectively. For the devices containing buffering additives and mannitol in the membrane, the rates of propranolol release were 1.5-times higher than those from the corresponding devices without mannitol (Fig. 3). With 100 or 75% of phosphate in dibasic form, the differences were significant ($p < 0.05$). However, the difference due to mannitol was much less than that caused by buffering agents.

Conclusions

We have described drug release from devices where solid-state salts of drugs with additives are entrapped between silicone membranes. The devices are readily formulated. The polar solid salts of the drug in the core do not partition to the polymer walls during storage and the initial burst in drug release is avoided. Salt forms of the drugs are also beneficial from the standpoint of drug stability. Drug release is activated by water and the rate of release can be controlled over a very large range with pH-adjusting agents in the device core if the unionized drug is sufficiently lipid soluble to partition in silicones.

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