International Journal of Pharmaceutics, 92 (1993) 177–181

IJP 03132

Dissolution medium independent release of propranolol from silicone reservoir devices [1]

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(Received 23 September 1992)
(Accepted 30 November 1992)

Key words: Propranolol; Silicone; Reservoir device; Controlled release; pH; Ionic strength; Osmotic pressure

Summary

The effect of aqueous dissolution medium properties on the release of model drug, propranolol, from water-activated and pH-controlled devices was investigated in vitro in diffusion cells. In the devices, powders of propranolol hydrochloride and pH-adjusting adjuvant, disodium phosphate, were entrapped between two silicone membranes. pH of dissolution medium ranged from 1.6 to 9.4, osmotic pressure from 138 to 950 mOsm/kg and ionic strength was 0.15 or 0.3. The osmolality and ionic strength of dissolution medium affected neither the inner pH and water content in the device nor the release of propranolol from the devices. When pH in the dissolution medium was raised, the inner pH of the device was increased slightly but not adequately to change propranolol release. Thus, the release of propranolol from the tested silicone reservoir devices was essentially independent of its environment.

Introduction

Drug release and dissolution may be influenced by the pH, osmolality and ionic strength of the dissolution medium (Doherty and York, 1989; Kohri et al., 1991, 1992; Soltero et al., 1991). In vivo many controlled release dosage forms are subjected to changing environmental conditions. For example, although the pH of the skin surface is mildly acidic (pH 4.2–5.6; Barry, 1983), during occlusion its pH may shift gradually from the acidic range to neutral (Aly et al., 1978). In the gastrointestinal tract, pH ranges from 1 to 4 in the stomach to 5 to 7 in the small intestine and mouth (Hui et al., 1987). Also, the osmolality and ionic strength can vary considerably in the GI tract.

Previously we described controlled release of weak acids (Sutinen et al., 1989) and weak bases (Sutinen et al., 1990) from water-activated and pH-controlled silicone reservoir devices. In the device, a solid-state salt of drug is entrapped with a buffering adjuvant between two silicone mem-

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[1] This study was partly presented at the 19th International Symposium on Controlled Release of Bioactive Materials, Orlando, FL, U.S.A., July 26–31, 1992.

branes. The drug release is activated by influx of water into the core of the device. In the core, water dissolves part of the drug and pH-adjusting adjuvant. Depending on the additive, pH of the device core is changed, and the impermeable, ionized drug is partly converted into a more permeable, unionized form which can penetrate through the silicone walls of the device (Sutinen et al., 1990). An initial burst of drug release can be avoided with this design. Constant zero-order release of drugs can be achieved, and the rate of drug release from the devices can be controlled over a wide range (740-fold) with suitable pH-adjusting agents in the device core if the unionized drug is sufficiently lipid-soluble to partition in silicones. To evaluate the feasibility of the water-activated and pH-controlled silicone device design for different and changing conditions, we investigated the influence of different dissolution media on propranolol release from the devices.

Materials and Methods

Preparation of the devices and buffer solutions

Silicone reservoir devices were made of Q7–4840 silicone A/B medical grade elastomer (Dow Corning, Midland, MI) as described earlier (Sutinen et al., 1990). 2 mg of both model drug, propranolol hydrochloride (Sigma, St. Louis, MO), and pH-adjusting agent, disodium phosphate (Merck, Darmstadt, Germany), were used in the devices. The thickness of the rate-limiting membrane in the devices was about 120 μm and the surface area of drug permeation 0.64 cm^2.

The effect of pH, ionic strength and osmolality of dissolution medium on the drug release was tested in buffer solutions with four different pH values, osmotic pressures and two different ionic strengths. pH 2.0 buffer solution consisting of HCl and KCl was prepared according to USP XXII. pH 4.7 buffer (0.1 M) solution was a mixture of acetic acid and sodium acetate and pH 7.4 (0.1 M) buffer solution was a mixture of sodium phosphate and disodium phosphate. pH 9.6 buffer solution was made of 0.1 M sodium carbonate adjusting the pH of solution to 9.6 with 0.3 M HCl. The ionic strength (μ) of the buffer solutions was adjusted to 0.15 or 0.3 with sodium chloride. The osmotic pressure (π) of the dissolution medium was determined with an osmometer (Osmostat OM-6020, Daiichi Kagaku, Kyoto, Japan) and adjusted to 138, 295, 550 or 950 mOsm/kg with sucrose. After the addition of sucrose the final pH values of the dissolution media were 1.6, 4.6, 7.3 and 9.4.

Solubility of propranolol

Solubility of propranolol in buffer solutions at pH 1.6, 4.6, 7.3 and 9.4 ($\pi = 550$ mOsm/kg, $\mu = 0.3$) was investigated by shaking propranolol hydrochloride suspension in the solvents. After equilibration, the saturated solutions were filtered. The concentration of propranolol in the filtrates was assayed by HPLC using a Beckman ultrasphere ODS column (3 μm, 45 × 4.6 mm; Beckman, San Ramon, CA). The mobile phase was a binary mixture of 25% (v/v) of acetonitrile and 75% (v/v) of acetic acid (pH 4.0). The detection wavelength was 289 nm, and at a flow rate of 1.0 ml/min, the retention time 2.4 min. Three parallel experiments were conducted in each case.

Drug release

The release of propranolol from the silicone reservoir devices in vitro was determined in side-by-side diffusion cells (DC-100, Crown Glass, Somerville, NJ) at 34 ± 1°C. The volume of dissolution medium was 3.0 ml. pH dependency of drug release was tested in pH 1.6, 4.6, 7.3 and 9.4 buffer solutions ($\mu = 0.3$, $\pi = 550$ mOsm/kg). The effect of osmolality of the dissolution medium was evaluated at pH 4.6 ($\pi = 295$, 550 or 950 mOsm/kg; $\mu = 0.15$) and at pH 7.3 ($\pi = 138$, 295, 550 or 950 mOsm/kg; $\mu = 0.3$). The influence of ionic strength on the release of propranolol was determined at pH 4.6 ($\mu = 0.15$ or 0.3; $\pi = 550$ and 950 mOsm/kg) and at pH 7.3 ($\mu =$ 0.15 or 0.3; $\pi = 138$ mOsm/kg).

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. At fixed times, samples of 250 μl were withdrawn or the receiving phase was completely changed to fresh buffer to maintain sink conditions. The concentration of propranolol in the samples was ana-

lyzed using HPLC as mentioned above. The apparent release rates of propranolol from the devices were determined as the slope of the released amount vs time plot after initial lag time. The release rates were normalised by the thickness of the rate limiting-membrane and the surface area of the release. Each experiment was repeated six times.

pH and amount of water in the devices

After release tests, devices were gently dried with a filter paper, weighed and the pH of the device core was measured using a microelectrode (Ross 8163, Orion Research, Boston, MA). The devices were dried at room temperature for a week and weighed. The amount of water absorbed in the devices was calculated as the weight difference between the wet and dried devices. Since the inner pH of the device containing propranolol hydrochloride and disodium phosphate was nearly constant between 24 and 72 h (Sutinen et al., 1990), the pH after release experiments can be used to characterize the inner pH of the device.

The statistical significance of the differences was assessed using one-way analysis of variance (ANOVA) followed by Fischer PLSD test. Values of $p < 0.05$ were considered to represent statistically significant differences.

TABLE 1

Effects of pH, osmotic pressure (π: mOsm / kg) and ionic strength (μ) of the dissolution medium on the rate of propranonol release (rate: % h^{-1} cm^{-1}) from the silicone reservoir device, the lag time of drug release (t_{lag}: h), the amount of water (H_2O: μl) in the device and the inner pH of the device (means ± SE of 4–6 experiments are presented)

Properties of dissolution medium			Propranolol release		Device properties (in 72 h)	
pH	π	μ	Rate	t_{lag}	H_2O	Inner pH
1.6	550	0.3	7.2 ± 0.9	23.2 ± 4.8	6.8 ± 0.5	6.4 ± 0.1
4.6	295	0.15	8.0 ± 0.2	10.1 ± 2.1 [c]	5.8 ± 0.4	–
4.6	550	0.15	7.0 ± 0.4 [a]	19.4 ± 1.5 [d]	7.4 ± 0.9	–
4.6	550	0.3	8.9 ± 0.5	7.5 ± 3.2 [e]	10.2 ± 1.7 [g]	6.3 ± 0.1
4.6	950	0.15	7.1 ± 0.5	13.0 ± 2.4	10.5 ± 1.0 [h]	7.0 ± 0.1
4.6	950	0.3	8.6 ± 0.7	16.3 ± 2.9	7.0 ± 1.8	–
7.3	138	0.15	10.6 ± 0.5	8.1 ± 2.2	8.7 ± 0.6	–
7.3	138	0.3	9.0 ± 0.8	12.9 ± 2.8	7.4 ± 0.5	–
7.3	295	0.3	8.5 ± 0.8	13.5 ± 3.4	8.9 ± 1.3	7.3 ± 0.2
7.3	550	0.3	7.8 ± 0.8	7.0 ± 2.2 [d]	7.2 ± 0.3	7.1 ± 0.1 [j]
7.3	950	0.3	8.8 ± 0.8	20.0 ± 3.1 [f]	7.4 ± 1.1 [i]	6.8 ± 0.1 [k]
9.4	550	0.3	6.0 ± 0.2 [b]	7.2 ± 0.1 [d]	8.6 ± 0.1	7.2 ± 0.1 [j]

[a] $p < 0.05$ compared to $\mu = 0.3$.
[b] $p < 0.05$ compared to pH 4.6.
[c] $p < 0.05$ compared to $\pi = 550$ mOsm/kg.
[d] $p < 0.05$ compared to pH 1.6.
[e] $p < 0.05$ compared to $\mu = 0.15$.
[f] $p < 0.05$ compared to $\pi = 550$ mOsm/kg.
[g] $p < 0.05$ compared to pH 1.6 and 7.3.
[h] $p < 0.05$ compared to $\mu = 0.3$.
[i] $p < 0.05$ compared to 295 and 550 mOsm/kg.
[j] $p < 0.05$ compared to pH 1.6 and 4.6.
[k] $p < 0.05$ compared to 295 and 550 mOsm/kg.
ANOVA followed by Fischer PLSD.

Results and Discussion

Effect of pH of dissolution medium

The rate of propranolol release from the silicone reservoir devices was practically independent of the pH of the dissolution medium (Fig. 1 and Table 1). However, the lag time before steady drug release was signifigantly longer at pH 1.6 than at other pH values.

Upon water absorption to the device, the resulting pH of the core determines the degree of ionization and, consequently, partitioning of propranolol to the silicone walls and the rate of propranolol release (Sutinen et al., 1990). When the pH values of the device core were adjusted to be 5.9–8.3 with different buffering additives, the rate of propranolol release was varied 23-fold and compared to unbuffered devices even 740-fold increase in drug release was obtained. In this study, the outer pH range of 1.6–9.4 caused only an upward shift of 0.8 pH units in the device core (Table 1). This small change in the core pH did not affect significantly the rate of propranolol release (Fig. 1 and Table 1). Thus, the drug release is controlled by the buffer conposition in the device core, and not by the pH of dissolution medium.

Due to the decreased ionization solubility of propranolol was much lower at pH 9.4 (0.5 mg/ml) than in other values of pH. Solubilities of propranolol hydrochloride varied at pH values 1.6, 4.6 and 7.3 from 19 to 94 mg/ml depending on the common ion effect in chloride containing medium, and this seemed to affect the rate of propranolol release. Although the pH of the device core was highest at pH 9.4, the steady-state rate of drug release was lowest with this buffer solution (Table 1). Possibly good partitioning of propranolol from the device core to silicone is compensated by the low solubility of propranolol on the surface of the device at 9.4.

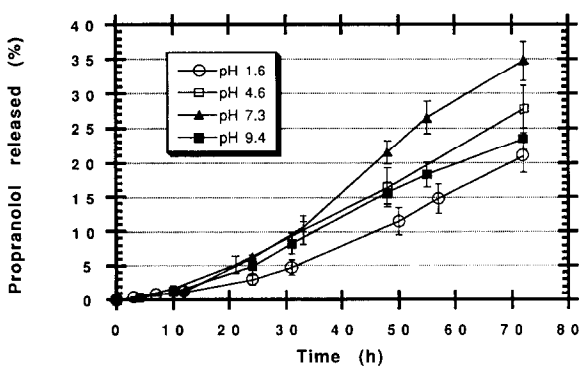

Fig. 1. The effect of pH of the dissolution medium on the release of propranolol from the silicone reservoir devices at 34°C. Means ± SE of 4–6 experiments are presented.

The average amount of water absorbed into the device during the release test was 7–10 μl. The moisture absorption capacity and the rate of water absorption into the device were not affected by the pH of the dissolution medium (Table 1). The amount of water in the core was adequate to dissolve the drug and pH-adjusting adjuvant and thus trigger drug release from the devices.

Effect of ionic strength and osmotic pressure

The change in the ionic strength of dissolution medium from 0.15 to 0.3 at pH 4.6 ($\pi = 550$ mOsm/kg) and at pH 7.3 ($\pi = 138$ mOsm/kg) affected neither the imbibition of water into the devices nor the resulting pH in the core (Table 1). Also, the release profile and rate of propranolol release from the silicone reservoir devices were independent of the ionic strength of the dissolution medium.

Surprisingly, the increase in the osmolality of dissolution medium from 295 to 950 mOsm/kg at pH 4.6 or from 138 to 950 mOsm/kg at pH 7.3 increased slightly the amount of water absorbed in the devices during the test and the rate of water absorption (Table 1). The influx of water into the core of the device is due to the gradient of osmotic pressure across the silicone membrane. Even an osmotic presssure of 950 mOsm/kg in the dissolution medium did not diminish the imbibition of buffer solution into the device core nor did it affect the release of propranolol from the devices. Also, the pH of the device core was practically unaltered (Table 1).

In conclusion, drug release from the water-activated and pH-controlled devices follows zero-order kinetics and is essentially independent of pH, osmotic pressure and ionic strength of dissolution medium. The independency of drug

release of the environment and the sufficient moisture absorbing capacity of the devices are promising features in the use of the system for oral and transdermal administration of drugs.

Ackowledgements

The authors wish to thank Mrs Lea Pirskanen for excellent technical assistance. This study was supported by Orion Corporation Farmos and the Technology Development Centre (TeKes), Helsinki, Finland.

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