Modification of the Dialysis Membrane Method for Drug Release from Suppositories

Masaru Yamazaki,[1,4] Soichi Itoh,[1] Naomi Sasaki,[1] Kazuhisa Tanabe,[2] and Mitsuru Uchiyama[3]

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INTRODUCTION

Three test methods for drug release from suppositories were compared in a previous paper (1). The apparatus of Muranishi *et al.* (2) (hydrophilic membrane filter SM11306, 0.45-μm pore size, Sartorius Gmbh, Germany) and that of Dibbern and Wirbitzki (3) (hydrophilic membrane, Durapore HVLP293-25, 0.45-μm pore size, Millipore Ltd., Japan) gave similar results.

The use of the apparatus of Tanabe *et al.* (4) (dialysis membrane, Spectra/Por 6 132542, molecular weight cutoff of 50,000, Spectrum Medical Ind., USA) allowed us to correlate the release rate and *in vivo* data (AUC, C_{MAX}, and T_{MAX} in rabbit). However, some problems occurred when using this apparatus: (i) failure to remove all water from the dialysis tubing retarded drug release from the suppository (4,5), and (ii) the rates of drug release from rectal capsules was slower than the values obtained with other methods (1).

EXPERIMENTAL

Materials

Indomethacin (JP grade) passed through a 200-mesh sieve. Pharmasol B-115 (equivalent to Witepsol H-15) and polyethylene glycol 4000 (JP) were gifts from Nippon Oil & Fats Co., Japan. A suppository mold formed of plastic was obtained from Kanae & Co., Ltd., Japan. All reagents were of analytical grade.

Indomethacin Suppositories

All suppositories used in this experiment contained 50 mg indomethacin. The preparation of experimental suppositories was described previously (1). The lot numbers of each commercial product (A, B, C, D, E, or F) were identical to those used previously (1).

[1] Faculty of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565, Japan.
[2] Kansai Rosai Hospital, Amagasaki, Hyogo 660, Japan.
[3] National Institute of Hygienic Sciences, Setagaya, Tokyo 158, Japan.
[4] To whom correspondence should be addressed.

Dialysis Tubing

The width of the available dialysis tubing (Spectra/Por 6 132542) varied, and we used only tubing of 28 ± 2 mm wide.

Suppository Drug Release Test

Figure 1 shows a sketch of our modified apparatus. It consists of a rack assembly made of stainless steel and a 1000-mL-tall beaker (Pyrex; 9.2-cm inside diameter, 20-cm height). The rack assembly consists of two agitator rings (each 80 mm in diameter, 60 mm in inside diameter, 4 mm thick, and about 65 g in weight), a bent wire (45 cm in full length, 3 mm thick, and about 28 g in weight), and a hanging clip (1.6 cm wide). The rings were held in a vertical position at 4.5-cm intervals by the wire. The moving device and the thermostatic arrangement were employed as a JP disintegration apparatus (Toyama Sangyo, Japan).

A 1000-mL volume of 50 m*M* phosphate buffer (pH 7.0) was placed in the flask as an immersion fluid and maintained at 37.0 ± 0.2°C. The surface of the fluid in the vessel was held at a height 15 cm above the bottom. The methods of sampling and analysis were described previously (1).

RESULTS AND DISCUSSION

Water Remaining in Dialysis Tubing After Squeeze

The tubing was cut in 17.0-cm sections, soaked in purified water for 24 hr, and rinsed. When the tubing was in-

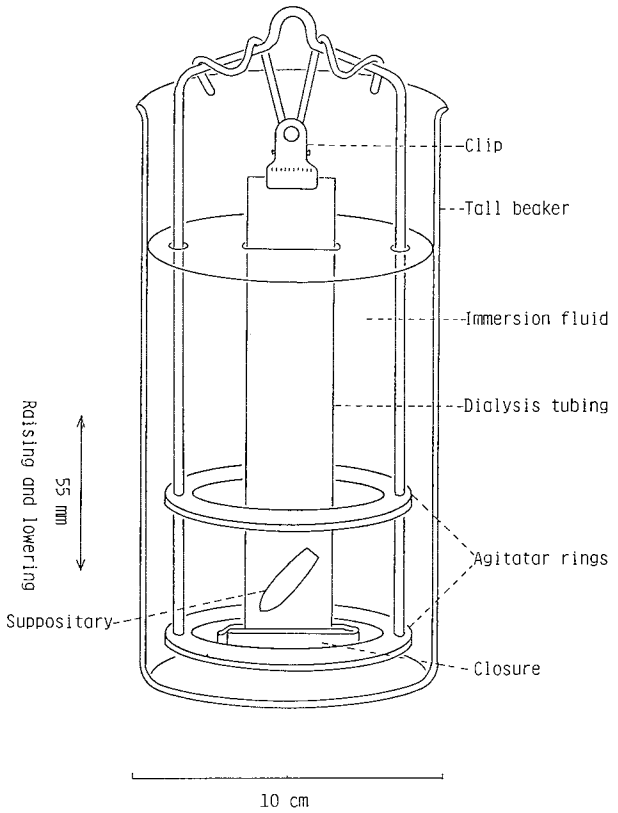

Fig. 1. Diagram of the apparatus used in the modified dialysis membrane method.

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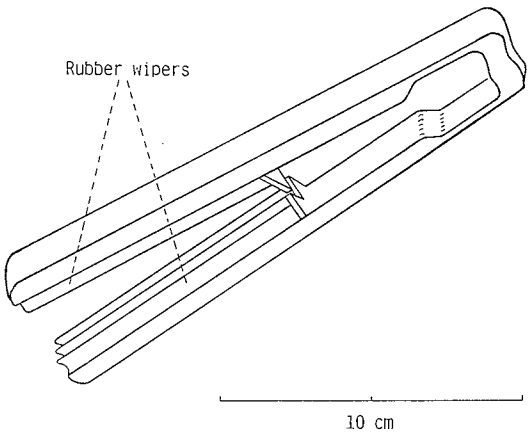

Fig. 2. A film squeegee.

serted between paper wipers (Kimwipe S-200) and the water squeezed out manually, water removal was incomplete. Similarly, two strokes with index and middle fingers, wearing rubber operating gloves, failed to remove the residual water (40 ± 19 mg water remaining in each segment, as determined by cutting the tubing open and removing residual water with a paper wiper).

We therefore used a film squeegee normally employed in a darkroom, made of plastic, about 18 cm long (Fig. 2) (King brand, Asanuma & Co., Japan, or Hama brand, Hama Co., Germany). The King squeegee has wide and soft rubber wipers, and therefore it was very easy to squeeze water, and the residual water amount was reduced to 9 ± 5 mg per tubing section.

After removing residual water with either the fingers or the film squeegee, drug release was measured from experimental oleaginous base suppositories. The percentages released in 6 hr did not differ in either case (69 ± 2%). After removing water with the film squeegee, we added water back to the tubing with a microsyringe. When more than 0.3 mL water was added to the tubing, the percentages released decreased to ~57%. Therefore, the effects of water remaining in the dialysis tubing were negligible using the film squeegee. The percentages released from water-soluble base suppositories were not affected by the addition of water (91 ± 2% in each case).

Modification of the Dialysis Membrane Method

In the method of Tanabe *et al.* (4), dialysis tubing is tied with thread, and consequently the end of the tubing wrinkles. The surface area of the tubing is not constant, and the inside liquid at the lower part of the tubing is not stirred satisfactorily. This problem was corrected by the use of a snap closure (Catalog No. 132736, Spectrum Medical Ind.) with a 5-g sinker (Fig. 1).

When we observed the rectal capsule in the tubing of the apparatus in the method of Tanabe *et al.* (4), the gelatin capsule gradually absorbed water and the inside surface of the tubing seemed to be coated with gelatin. More agitation applicable to this release test was needed.

We then used a JP (or USP) disintegration apparatus as a moving device. A suppository was dropped into the dialysis tubing, which was hung on the rack assembly (Fig. 1), and the assembly was immersed in a tall beaker and moved vertically, avoiding any horizontal motion or movement of the axis from the vertical. Any air remaining in the tubing was expelled by the water pressure. An oleaginous base suppository melted rapidly and the molten suppository spread in the tubing. While a water-soluble base suppository absorbed water and the content volume swelled, the capacity of the tubing is more than 30 mL. A rectal capsule was broken by water pressure and up-and-down motion and released the contents of the capsule.

Mixing tests with blue ink indicated that the stirring was accomplished satisfactorily.

Release Profiles of Eight Indomethacin Suppositories

Table I shows the percentages released using the mod-

Table I. Percentages Released for Indomethacin Suppositories by the Modified Dialysis Membrane Method

Suppository	Percentage released[a] (n = 5)		
	In 2 hr	In 4 hr	In 6 hr
Oleaginous base suppository			
Experimental	40.9 ± 2.4 (5.9)	59.3 ± 2.1 (3.5)	69.7 ± 2.1 (3.0)
Product A	50.1 ± 4.9 (9.8)	71.5 ± 4.9 (6.9)	82.1 ± 4.9 (6.0)
Product B	44.1 ± 3.0 (6.8)	70.5 ± 5.2 (7.4)	85.6 ± 3.7 (4.3)
Product C	38.3 ± 1.1 (2.9)	53.0 ± 1.0 (1.9)	61.5 ± 1.2 (2.0)
Water-soluble base suppository			
Experimental	44.3 ± 2.6 (5.9)	72.2 ± 1.9 (2.6)	90.1 ± 1.9 (2.1)
Product D	40.3 ± 3.0 (7.4)	68.1 ± 2.3 (3.4)	83.8 ± 2.2 (2.6)
Rectal capsule			
Product E	20.0 ± 4.5 (22.5)	38.2 ± 8.5 (22.3)	54.9 ± 11.4 (20.8)
Product F	16.9 ± 2.2 (13.0)	34.2 ± 3.3 (9.6)	46.2 ± 2.9 (6.3)
(Range/Median)	(33.2/40.6)	(38.0/63.7)	(43.9/75.9)

[a] Average ± SD (coefficient of variation).

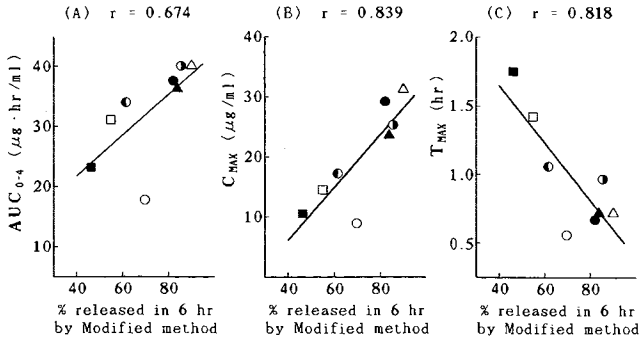

Fig. 3. Correlation (A) between AUC_{0-4} (area under the plasma concentration–time curve from 0 to 4 hr in the rabbit) and the percentage released in 6 hr from indomethacin suppositories; (B) between C_{MAX} (maximum plasma concentration) and the percentage released; (C) between T_{MAX} (maximum concentration time) and the percentage released. r is the regression coefficient. (○) Experimental suppository; (●) Product A; (◑) Product B; (◐) Product C; (△) experimental suppository; (▲) Product D; (□) Product E; (■) Product F. Circles, triangles, and squares represent oleaginous base suppositories, water-soluble base suppositories, and rectal capsules, respectively.

ified method. The drug was released more rapidly from the suppositories by the modified method than by the method of Tanabe *et al.* (1), and the percentages of two rectal capsules tested by this modified method were twice those tested by the method of Tanabe *et al.* (1).

Figure 3 shows the correlation between the percentages released in 6 hr by the modified method and the *in vivo* parameters in the rabbit (1). The data obtained by the modified method correlated well with the *in vivo* parameters. Except for the experimental oleaginous suppository, the regression coefficients for AUC_{0-4}, C_{MAX}, and T_{MAX} were 0.935, 0.959, and 0.922, respectively. There was a linear relationship between the *in vivo* parameters and the percentages released from seven suppositories, except for the experimental oleaginous base suppository. This suppository does not contain any excipient, such as surfactant, suspending agent, or adjuvant for absorption, which may account for our results.

In conclusion, this modified method is easy to perform. There is no need to deaerate the fluid, which may cause problems with other methods.

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