# Zero-Order Release from Cylindrical Xerogel Preparation

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**The objective of this study was to prepare and evaluate the possibility of cylindrical xerogel preparations with zero-order release characteristics. As model polymers, polyvinyl alcohol (PVA), hydroxypropyl methylcellulose (HPMC), and acrylic block copolymers of methacrylic acid and the methacrylate, Eudispert, were selected and formed into xerogel formulations. Tegafur, 5-fluorouracil (5-FU), aspirin, benzoic acid, *p*-methoxybenzoic acid, theophylline, and salicylamide were employed as model compounds and thereby incorporated into xerogel matrices.**

**In a dissolution test (rotating basket method; pH 7.4), PVA xerogel did not erode nor swell in dissolution medium, and did not exhibit zero-order release, but rather exhibited Fickian's law diffusion followed by the initial burst release profile. In the case of HPMC xerogel, swelling of the polymer was observed to some extent, but the release profile was almost the same as PVA, suggesting the Fickian diffusion of drug from HPMC gel; in contrast, Eudispert gel showed zero-order release in every drug. The polymer was also gradually dissolved into the medium at a zero order release rate.**

**Finally, the Eudispert xerogel containing theophylline was orally administered to beagle dogs, and plasma was withdrawn periodically. The sustained-release characteristics were observed and the possibility of the cylindrical xerogel preparation for oral usage was demonstrated.**

**Key words** xerogel; polyvinyl alcohol; hydroxypropyl methylcellulose; acrylic polymer; zero-order release; theophylline

Significant advances have been made recently in the fields of controlled release delivery systems. The concept has led to many pragmatic applications for the delivery of a number of drugs or active reagents.[1,2] Gel formulation seems so attractive since it is applicable for a variety of administration routes,[3—5] for example, orally, rectally, subcutaneously, and dermally. We reported earlier on a novel rectal gel preparation comprising block copolymers of methacrylic acid and methacrylate.[6] In that study, rectal gel preparations showed excellent staying or bioadhesive effects in the lower part of the large intestine in animals compared with control suppositories. Nevertheless, no *in vitro* release characterization was made. If the *in vitro* release characteristics are well optimized in addition to the above advantages of water solubility and bioadhesiveness, an ideal sustained-release formulation might be possible.

In the present study, therefore, we prepared a cylindrical xerogel preparation, and evaluated its *in vitro* release characteristics. As model polymers, polyvinyl alcohol (PVA), hydroxypropyl methylcellulose (HPMC), and acrylic block copolymers of methacrylic acid and methacrylate, Eudispert, were selected and formed into xerogel formulations. Finally, optimized xerogel made of Eudispert containing theophylline as a model drug for oral usage was orally administered to beagle dogs and the *in vivo* capability as a sustained-release dosage form was also examined.

## Experimental

**Materials** Tegafur, 5-fluorouracil (5-FU), aspirin, benzoic acid, *p*-methoxybenzoic acid, theophylline, and salicylamide, were obtained from Nacalai Tesque Co., (Kyoto). Eudispert mv was donated by the Higuchi Company (Tokyo). PVA (polymerization degree=2500) , and HPMC 2910 was supplied by Shin-etsu Kagaku Co., Ltd., (Tokyo). Other reagents were all of reagent grade, special.

**Preparation of Xerogels** PVA : 10 g of PVA was dissolved into 87.5 g of pH 7.4 phosphate buffer (80 °C) and 2.5 g of drug solution was added. The solution was placed in a syringe and freeze dried at minus 20 °C for 12 h. The sample remained at room temperature for another 12 h. This procedure was repeated four times to form PVA gel.

HPMC: 2.5 g of drug solution was poured into 87.5 g of pH 7.4 phosphate buffer (80 °C), 10 g of HPMC was added and temperature of this mixture was gradually lowered to room temperature under agitation to form gel.

Eudispert: The preparation of xerogel was produced by the freeze-drying method reported previously.[6] Twenty grams of Eudispert mv was suspended in 66.1 g of drug solution, and agitation continued in NaOH solution until gelation was completed. The prepared hydrogel (2.0 g) was put into a polypropylene syringe with an inside diameter of 9 mm, and frozen for 12 h at minus 20 °C. This gel was then freeze-dried for another 12 h to form xerogel.

**Evaluation of Medium Uptake Rate and Erosion Rate of Xerogels** PVA, HPMC and Eudispert mv xerogel were incorporated into a dialysate tube (32 mm×20 mm×0.031 mm (thickness)). The rotating basket method in JPXIII was applied to the sample. Nine hundred ml of medium (pH7.4) was used in the test, the temperature was maintained at 37 °C, and the rotating speed was fixed at 100 rpm. The sample was picked up periodically and weight of the gel was determined. The weight of absorbed water per weight of dried xerogel was adopted as a criterion for medium uptake.

The amount of polymer dissolved was evaluated as follows. In determining of HPMC, the phenol–sulfuric acid method was adopted as described in previous paper.[7] In the case of Eudispert, to 5 ml of withdrawn sample solution, the same amount of 0.1 N HCl solution was added and allowed to remain for 24 h. The precipitated Eudispert was filtered through a membrane filter (cellulose nitrate type, 0.45 $\mu$m, 25 mm$\phi$). Residue on the membrane filter was washed with another 50 ml of water, and then dried at 60 °C for 4 h. The increased weight was assessed as dissolved polymer weight. A similar method to that of Eudispert was employed for PVA. Acetone was added to precipitate the polymer instead of the 0.1 N HCl used in the case of Eudispert; the other processes were essentially the same.

**Release Test** The rotating basket method was employed, and 900 ml of pH 7.4 phosphate buffer was used, the rotating speed was fixed at 100 rpm and the temperature was maintained at 37 °C. UV absorption for the withdrawn sample was measured in relation to drugs. Benzoic acid (225 nm), *p*-methoxybenzoic acid (240 nm), aspirin (225 nm), salicylamide (295 nm) theophylline (270 nm), tegafur (270 nm), and 5-FU (270 nm) concentrations were determined.

**Determination of Drug Solubilities** Excess drug amount was sus-

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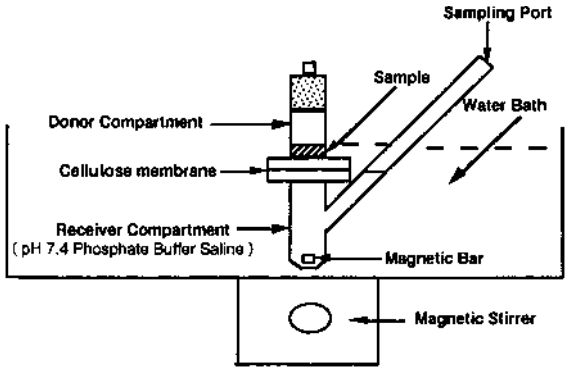


Fig. 1. Apparatus for Loveday Type Diffusion Cell

pended in pH 7.4 phosphate solution and maintained at 50 °C for 2 h, then incubated for 24 h at 37 °C. The suspension was centrifuged at 3000 rpm for 10 min, the supernatant was filtered, diluted and concentration of the supernatant was determined.

**Calculation of Apparent Diffusion Coefficient** The diffusion coefficient of model drugs was calculated as described in the previous report.[8] The prepared gel (HPMC, Eudispert) was put on the surface of a donor site of Loveday-type cell sandwiching cellulose membrane and the drug diffused into the receiver site was periodically withdrawn from the sampling port as shown in Fig. 1. Diffusion coefficient was calculated using the following equation.

$$Q=2\sqrt{(2A-Cs)\times Cs\times D\times t} \quad (1)$$

$Q$ means the cumulative released amount at time $t$, $A$ means drug concentration in HPMC and Eudispert gels, $Cs$ and $D$ are the drug solubility and diffusion coefficient, respectively. In this experiment, the adsorption of drugs to cellulose membranes could be neglected.

***In Vivo* Evaluation of Eudispert Xerogel Formulations** Special hard gelatin capsules (1/80 oz, J type, Kasho Co., Tokyo, Japan) filled with theophylline powder (100 mg), corresponding Eudispert xerogel, Theodur (100 mg) or Theolong (100 mg) as sustained-release products, were administered orally to male beagle dogs with 30 ml of water. The plasma concentration of theophylline was determined by HPLC method that was slightly modified from Kester's method.[9] The area under the curve ($AUC_{0-10}$) was calculated using trapezoidal rule.

## Results and Discussion

**The Ability of Medium Uptake and Erosion Rate of Polymer Made of Xerogel** Figures 2A, and 2B show the ability of medium uptake: swelling ability, and erosion rate of polymer made of xerogels, respectively.

As shown in Fig. 2A, PVA xerogel did not absorb buffer medium at all. In the case of HPMC xerogel, the uptake of test medium was comparatively large in the initial phase, swelling was almost completed within 4 h and but then the extent of swelling gradually increased further up to 8 h. For HPMC, Ford mentioned its rapid hydration followed by swelling as protective gel layer[10]; this phenomenon well coincided with the HPMC data demonostrated in the present study, whereas Eudispert gel took up test medium at an almost constant rate. Visual observation of xerogels in the buffer medium showed they well coincided with the uptake volume of test medium. For example, PVA xerogel did not swell in the medium, while Eudispert xerogel did show swelling.

Figure 2B shows the erosion rate of polymer made of xerogel. As shown in Fig. 2A, since PVA xerogel did not absorb the buffer medium at all, PVA was not expected to dissolve into the buffer medium. In fact, the erosion level of PVA remained at a negligible level. The experimental data well coincided with our expectations.

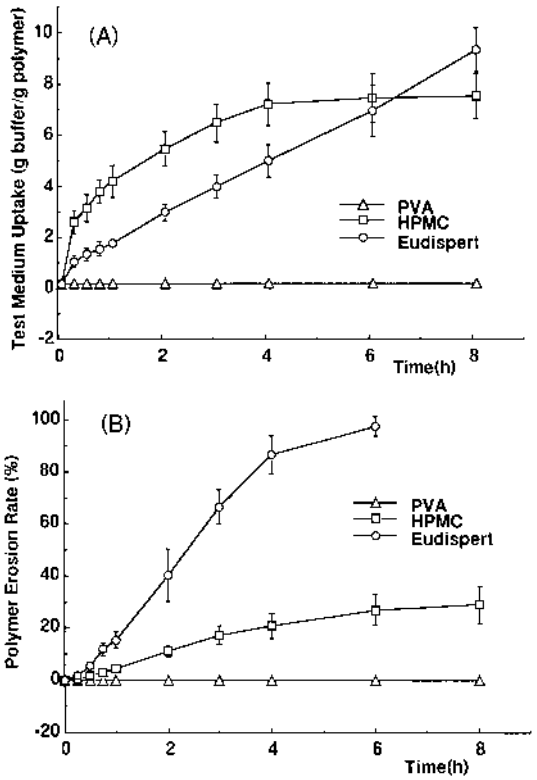


Fig. 2. Test Medium Uptake (A) and Erosion Ratio of Various Polymers (B) of PVA , HPMC, and Eudispert Gels

Each point represents the mean±S.D. of three experiments.

Eudispert xerogel was found to erode or decompose in the test medium at a comparatively rapid release rate. Its eroding rate was almost constant until almost 90% of the drug had been released (the time was almost 4 h). In the case of HPMC gel, the eroding profile shows the first-order dissolution profile, not the zero-order release, and only a some portion (nearly 30%) of the polymer was dissolved in the medium.

***In Vitro* Release from PVA, HPMC, and Eudispert Xerogel** Figures 3A, B, and C show the release profiles of various drugs from PVA, HPMC and Eudispert xerogel formulations, respectively.

As shown in Fig. 3A, the release of various drugs from PVA xerogel was comparatively fast. Almost 40 to 80% of drugs were released at 1 h, so that the release profile seems to exhibit Fickian's law of diffusion, not the zero-order. In the case of HPMC xerogel, the formulation showed a simultaneous release profile, accompanied by swelling. But the release amounts of each drug at 1 h were less than those released from PVA xerogel. In PVA xerogel, a portion of drug incorporated into PVA matrix might be precipitated as crystals during the repeated freeze drying process. In addition, the burst release of drug from PVA xerogel seems to be due to initial dissolution of the drug incorporated in the surface area of prepared gel since PVA xerogel could not absorb water nor erode in the medium as shown in Fig. 2A and Fig. 2B. Eudispert xerogel, in contrast, shows zero-order release in every drug, even though initial release rates were a little different among model drugs. In fact, linear correlation coefficient values for tagfur, 5-FU, *p*-methoxybenzoic acid, theo-

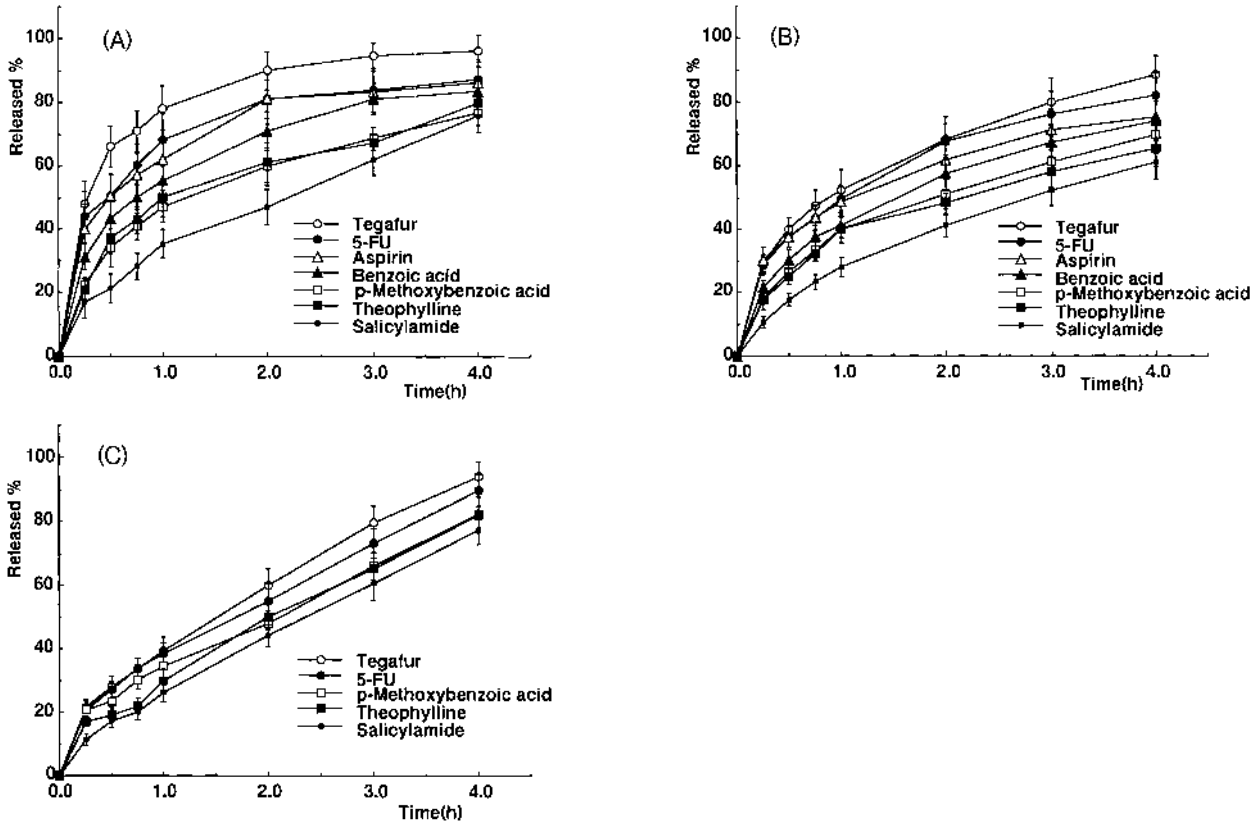


Fig. 3. Drug Releasing Profiles from PVA (A) , HPMC (B), and Eudispert (C) Xerogels Containing 2.5% of Drug

Each point represents the mean±S.D. of three—four experiments. For Eudispert gels containing aspirin and benzoic acid, the gelation was incomplete. Therefore, these two drugs were not employed in the dissolution test.

phylline, and salicylamide, calculated using the dissolution data between 15 min and 4 h (see Fig. 3C), were 0.997, 0.999, 0.998, 0.997, and 0.999, respectively.

There are some zero-order release systems such as case-II transport[11] and the megaloporous system.[12] The case-II transport system is accompanied by zero-order release with a swelling controlled system by transition of the glassy polymer to gelly polymer. Whereas Hann and Lerk[12] proposed the megaloporous system which is composed of two phases with different liquid-penetration properties and delivers most of its drug content at a constant rate. Its zero-order release was based on the concept of a decrease in the rate of surface area exposure in time of the restraining matrix phase to the penetration liquid with a simultaneous increase in time of the total restraining matrix phase surface area, contributing to the drug delivery. Nevertheless, the zero-order release observed in Eudispert xerogel could not be explained by either of the above two models in a release mechanism. In Eudispert xerogel, the release rates of zero-order release phase resembles that shown in Fig. 3C. The release rates of drugs are the same as the eroding or dissolution rates of Eudispert polymer itself. This phenomenon suggests that zero-order release from the Eudispert xerogel system was caused by eroding the polymer from cylindrical xerogel at a constant rate, and suggesting eroding or disintegration of the Eudispert polymer is the rate limiting step of drug dissolution in this system. Even though the detailed zero-order release mechanism could not resolved in the present study, another examination will be performed in the near future.

The drug release rates from PVA and HPMC xerogel were very different among model drugs as shown in Figs. 3A and 3B. Table 1 also summarizes solubilities (37 °C) and apparent diffusion coefficients for model drugs used in the present study. The release rate of model drugs from PVA and HPMC xerogel seems to be proportional to its solubility data. In the case of HPMC xerogel, the rate limiting step seems to be penetration of water into the gel matrix and the drug diffusion through the swollen gel matrix, whereas the initial burst release from PVA gel seems to the drug incorporated in the surface area of the cylindrical gel, since PVA could not absorb water nor erode in the medium.

In conclusion, release characteristics of three different type xerogels were examined and the zero-order release pro-

Table 1. Solubilities and Diffusion Coefficients of Drugs Used in the Present Study

| Drug | Solubility[a] (mg/ml) | Diffusion coefficient ($cm^2/sec$)[b] | |
|---|---|---|---|
| | | in HPMC hydrogel | in Eudispert hydrogel |
| Tegafur | 27.9 | $12.55\times10^{-7}$ | $13.74\times10^{-7}$ |
| 5-FU | 16.0 | $7.21\times10^{-7}$ | $6.65\times10^{-7}$ |
| Aspirin | 15.8 | $7.84\times10^{-7}$ | $8.82\times10^{-7}$ |
| Benzoic acid | 9.2 | $3.36\times10^{-7}$ | $5.43\times10^{-7}$ |
| *p*-Methoxybenzoic acid | 6.6 | $3.32\times10^{-7}$ | $4.85\times10^{-7}$ |
| Theophylline | 5.6 | $4.44\times10^{-7}$ | $6.71\times10^{-7}$ |
| Salicylamide | 2.2 | $3.82\times10^{-7}$ | $5.51\times10^{-7}$ |

All values are mean of 2—4 experiments. *a*) Solubility in pH 7.4 buffer at 37 °C. *b*) Diffusion coefficient at 37 °C.

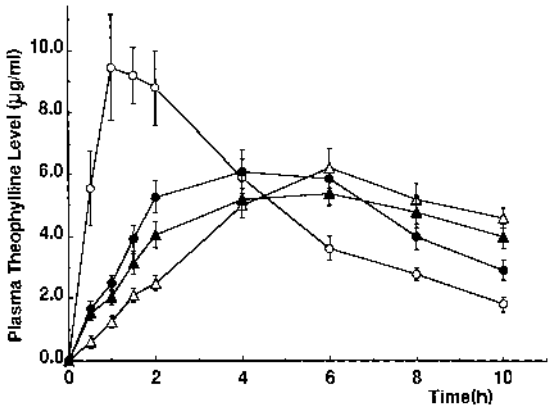


Fig. 4. Plasma Theophylline Levels after a Single Oral Administration of Powder (○), Eudispert Xerogel (▲), Theodur (△) and Theolong (●) in Beagle Dogs (100 mg/body)

Each point represents the mean±S.D. of four beagle dogs and vertical lines indicate the standard deviation.

files were confirmed in related to Eudispert xerogel.

***In Vivo* Evaluation of Eudispert Xerogel Containing Theophylline** Sustained-release preparations seems very useful to avoid severe adverse effects and obtain the maximum therapeutic effect. Theophylline was selected as a model compound since several sustained-release products containing theophylline have been applied to a number of patients suffering from asthma. Figure 4 illustrates the plasma theophylline level in beagle dogs following a single oral administration of theophylline powder in a conventional dosage form, Eudispert xerogel, and sustained-release tablets (Theolong, Theodur) as a positive control. The Eudispert xerogel containing theophylline showed a sustained-release profile. In addition, a plateau plasma theophylline level was obtained for a long period (between 4—10 h). The $AUC_{0—10}$ for the Eudispert xerogel ($AUC_{0—10}$ was 43.2±3.9 $\mu$g·h/ml) was not significantly different from $AUC_{0—10}$ of Theolong (45.5± 4.9 $\mu$g·h/ml) or Theodur (42.8±3.0 $\mu$g·h/ml). This suggested the potential for oral usage of the xerogel preparation.

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