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## Sustained Release of Sulfamethizole from Agar Beads after Oral Administration to Humans<sup>1)</sup>

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The use of agar beads for sustained release of a urinary tract disinfectant was examined *in vivo*. Agar beads containing dispersed sulfamethizole were administered to five healthy volunteers, and the rate of excretion of the drug in urine was determined for pharmacokinetic analysis. The results indicated that agar beads should be useful for the preparation of sustained release dosage forms.

**Keywords**—sulfamethizole; agar beads; sustained release; release rate; agar content; bead size; oral administration; urinary excretion; pharmacokinetic analysis; dosage form

In order to prolong the drug action and to avoid excessive drug concentrations in plasma and tissues, the use of synthetic membranes for controlled release of bioactive compounds has recently been investigated.<sup>3-5)</sup>

Some natural polymers may be suitable for use in controlled release dosage forms. For example, the use of polysaccharides such as konjac, a glucomannan, has been examined in connection with dosage form design for sustained drug release.<sup>6)</sup> Furthermore, the use of agar, the polysaccharide complex extracted from certain marine algae of the class *Rhodophyceae*, in controlled-release dosage form design has been examined *in vitro* in this laboratory.<sup>7)</sup> It appeared that agar beads were suitable as a vehicle for sustained release of drugs.

In the present study, the control of drug release by changing the agar content and the bead size was examined by measuring the rate of excretion of a urinary tract disinfectant in urine after oral administration to humans. The urine data were analyzed pharmacokinetically.

### Experimental

**Materials**—Powdered agar was of first grade, Japanese Industrial Standard, purchased from Wako Pure Chemical Industries, Osaka. Water content and total ash as determined according to the test procedures described in the Japanese Pharmacopeia were 1.67% and 2.45% (dry weight basis), respectively. Sulfamethizole was of Japanese Pharmacopeial grade from Eisai Co., Tokyo. Hydrochloric acid, sodium chloride, sodium phosphate dibasic, and sodium nitrite were purchased from Wako Pure Chemical Industries, Osaka, while ammonium sulfamate and Tsuda reagent were purchased from Tokyo Kasei Kogyo Co., Tokyo and

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from Junsei Pure Chemicals Co., Tokyo, respectively. Except for ethyl acetate, which was distilled, other materials were of reagent grade and were used without further purification.

**Preparation of Agar Beads**—Procedures for the preparation of the agar beads were described in the previous report.<sup>7)</sup> By this method, dried beads about 3 mm in diameter were obtained. To obtain beads with a smaller diameter, a plastic syringe with a needle (gauge No. 16 or 18) was employed, and the beads were dried before sieving. The drug contents of the dried beads were about 57%.

**Measurement of Release Rates**—Twenty beads containing sulfamethizole were added to 100 ml of release medium kept at 37° in a 125 ml wide-mouthed bottle in a constant temperature water bath. The release medium was J.P. IX disintegration medium No. 1 at pH 1.2. The bead suspension was stirred with a magnetic stirring button (2 cm in diameter) by means of a submersible magnetic stirrer (Acrobat Stirrer, MS Instruments, Osaka) at a rate of about 250 rpm. At suitable intervals, a 1 ml portion of the medium was pipetted out and diluted with 0.05 M Na<sub>2</sub>HPO<sub>4</sub> prior to absorbance measurements at 262 nm using a digital spectrophotometer (model 200-20, Hitachi Manufacturing Co., Tokyo). Release studies were carried out in duplicate and the average values are plotted in the figures.

**In Vivo Study Protocol**—Five healthy male volunteers, 23—31 years of age and weighing 51—65 kg, received a commercial uncoated tablet (Urocydal, sulfamethizole content of 250 mg, Eisai Co., Tokyo) or agar beads containing 250 mg of sulfamethizole, with 200 ml of water. The agar beads were prepared from 5% agar in water and had an average diameter of 0.68 mm after drying. Each preparation was administered in a completely randomized crossover design with a 1-week rest between administrations.

All subjects were fasted for 10 hr before and 4 hr following the drug administration. Urine samples were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 hr. At each time, the urine volume was recorded. The urine samples were stocked at 4° until analysis. The urine samples were assayed by the modified Bratton-Marshall procedure.<sup>8)</sup>

**Pharmacokinetic Analysis**<sup>9)</sup>—The excretion rate of an unmetabolized drug following oral administration can be expressed by the following equation;

$$\frac{dA_u}{dt} = \frac{k_{ex}k_a f D_0}{k_a - k_{el}} (e^{-k_{el}t} - e^{-k_a t})$$

where  $dA_u/dt$  = excretion rate,  $k_{ex}$  = urinary excretion rate constant,  $k_a$  = absorption rate constant,  $f$  = fraction of the dose absorbed,  $D_0$  = dose and  $k_{el}$  = elimination rate constant. Apparent elimination rate constants were obtained from the elimination phase of a log excretion rate *vs.* time plot based on the following equation,

$$\log \left( \frac{dA_u}{dt} \right)_{\text{elimination}} = - \frac{k_{el}}{2.303} t + \log \frac{k_{ex}k_a f D_0}{k_a - k_{el}}$$

while apparent absorption rate constants were obtained from a plot of the residuals in a log excretion rate *vs.* time plot based on the following equation;

$$\log \left( \frac{dA_u}{dt} \right)_{\text{residual}} = - \frac{k_a}{2.303} t + \log \frac{k_{ex}k_a f D_0}{k_a - k_{el}}$$

## Results and Discussion

Some oral sustained release preparations reportedly fail to release all of the drug during their passage through the gastrointestinal tract. Since the period during which preparations pass through the gastrointestinal tract is considered to be about 8 hr,<sup>10)</sup> sustained release preparations should ideally release all of the drug in 8 hr.

### Control of Drug Release by Changing the Agar Content

In contrast with the rapid dissolution from the sulfamethizole tablet, sustained release was obtained from the agar beads (Fig. 1). As the agar content was decreased, the release rate increased. It appears that an increase in agar content resulted in denser matrices, decreasing the rate of travel of drug molecules through the beads.

### Control of Drug Release by Changing the Bead Size

The average diameters of the beads were 0.68, 1.88 and 2.99 mm. As shown in Fig. 2, the agar beads with a small diameter released the drug faster than those with a larger diame-

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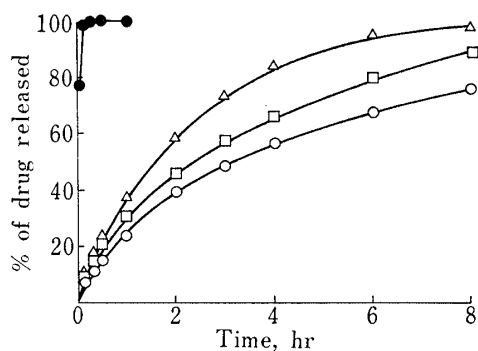


Fig. 1. Release Profiles of Sulfamethizole from Agar Beads of Various Agar Contents in J.P. Disintegration Medium No. 1 at pH 1.2 and 37°

Key; ●, Tablet; ○, 7.5%; □, 5%; △, 3% agar beads.

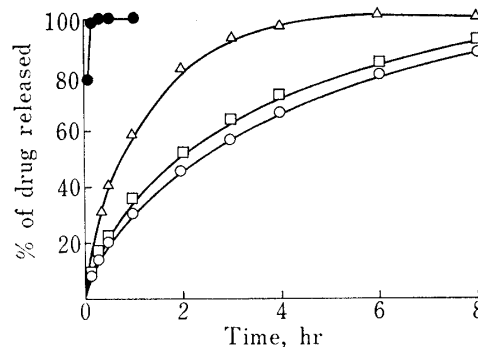


Fig. 2. Release Profiles of Sulfamethizole from Agar Beads of Various Diameters in J.P. Disintegration Medium No. 1 at pH 1.2 and 37°

Key; ●, Tablet; ○, 2.99 ± 0.26 mm; □, 1.88 ± 0.04 mm; △, 0.68 ± 0.02 mm agar beads.

ter. As expected from Higuchi's equation,<sup>11)</sup> a decrease in diameter caused an increase in the exposed area, and the rate of drug release was increased.

### *In Vivo* Studies in Humans

Agar beads of various diameters were administered to one volunteer, and the cumulative amounts of drug excreted in urine were compared. The results are shown in Table I. The bioavailability of the drug from the three preparations was less than that from the tablet, but the preparation 0.68 mm in diameter seemed to provide acceptable bioavailability compared with the tablet. Thus, agar beads 0.68 mm in diameter were administered to five healthy volunteers. The excretion rate is plotted against time in Fig. 3. The maximum excretion rate was low and the excretion pattern was delayed but extended to 10 hours after administration of the agar beads, in contrast to the higher excretion rate during the initial period and shorter (8 hours) excretion period following administration of the tablet. Sustained excretion is a reflection of the sustained blood level profile due to slow absorption, which in turn is attributable to sustained release of the drug from the agar beads. Excretion rate data were analyzed pharmacokinetically. The elimination and absorption rate constants obtained are listed in Table II. The smaller absorption rate constant following administration of the agar beads probably results from sustained supply of the drug to the plasma due to sustained absorption.

Fig. 4 shows the cumulative amounts of sulfamethizole excreted in urine. The urinary recovery of the drug in 12 hr was 87% of the dose in the case of the tablet and 78% of the dose in the case of the agar beads. The characteristic excretion profile of the drug following admin-

TABLE I. Bioavailability of Sulfamethizole following Oral Administration of 250 mg as a Tablet or in Agar Beads of Various Diameters

Diameter (mm)	Amount of drug excreted (mg)	Amount excreted
		Amount excreted from tablet
Tablet	230.7	1.00
0.68 ± 0.02	205.3	0.82
1.88 ± 0.04	169.4	0.74
2.99 ± 0.26	130.6	0.57

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TABLE II. Comparison of Absorption and Elimination Rate Constant obtained after Administration of Sulfamethizole as a Tablet or in Agar Beads

	$k_a$ , hr <sup>-1</sup>	$k_{el}$ , hr <sup>-1</sup>
Tablet	1.32	0.67
Agar beads	0.86	0.48

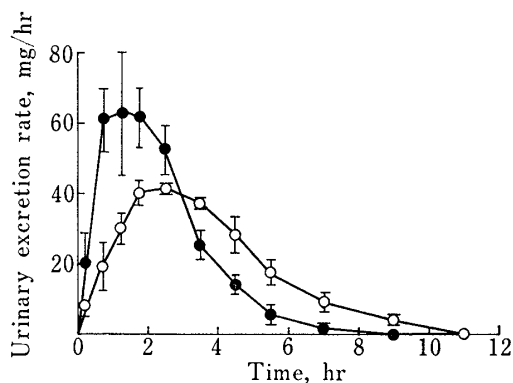


Fig. 3. Effect of Dosage Form on the Excretion Rate of the Drug following Oral Administration of 250 mg of Sulfamethizole as a Tablet (●) or in Agar Beads (○)

Average of five volunteers with SEM.

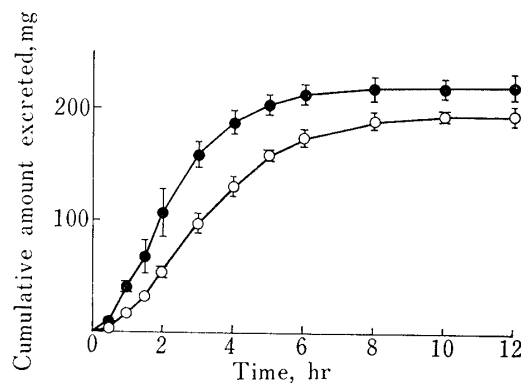


Fig. 4. Effect of Dosage Form on the Cumulative Amount excreted in Urine following Oral Administration of 250 mg of Sulfamethizole as a Tablet (●) or in Agar Beads (○)

Average of five volunteers with SEM.

istration of the agar beads is a sustained excretion pattern with rather small variability in the excretion rates among individuals (see Fig. 3), though disadvantages in the use of the agar beads include slow excretion during the initial period and some reduction in bioavailability. Thus, a combination of a rapidly dissolving preparation with agar beads containing sulfamethizole may be useful for the treatment of urinary tract infections.

The above results indicate that agar beads should be useful for the preparation of sustained release dosage forms. The use of the agar beads for sustained release of other drugs is being examined in our laboratory.