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Preparation and Evaluation of Gelatin Microcapsules of Sulfonamides[1)]

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A simple microencapsulation of three sulfonamides (sulfanilamide, sulfisomidine and sulfamethizole) was investigated. The preparation is based on dispersion of a gelatin–sulfonamide mixture in liquid paraffin, followed by drying and hardening with formalin–isopropanol treatment. The microcapsules were recovered as a discrete, free-flowing powder with a particle diameter of 250—840 μm. Dissolution of sulfamethizole from microcapsules approximated a zero-order release pattern from 0 to 10—30% dissolution. These microcapsules may be useful for studies related to sustained-release formulation.

Keywords——microencapsulation; sulfonamide; gelatin; dissolution test; particle-size analysis; sustained-release formulation

In recent years, microencapsulation has been increasingly used in pharmaceuticals owing to the clinical and therapeutic advantages offered by this process.[2,3)] Gelatin encapsulation is the oldest and perhaps the most commonly used. Gelatin can be easily digested by the human gastrointestinal juice, and its rate of hydrolysis can be modified by hardening. The encapsulation procedure reported here is a drying method in solution, employing formalin–isopropanol treatment to enhance the hardness of the gelatin microcapsules.[4)] This paper also reports on the *in vitro* dissolution rate of gelatin capsules prepared by this technique.

Experimental

Microencapsulation——The basic encapsulation procedure is outlined in Chart 1. The sulfonamides (sulfanilamide, sulfisomidine and sulfamethizole) were passed through a J.P. No. 100 sieve (less than 149 μm in diameter) before encapsulation. One-hundred and twenty-eight grams of water were added to 38 g of gelatin (Gelatin weiß, Merck) at 55—60 °C with stirring. After being allowed to stand at room temperature for 24 h, the gelatin had swollen completely. This swollen gelatin solution was refrigerated for 24 h at 2—5 °C. The batch changed from a viscous solution to a hard gel. The gel was cut into 1×1 cm cubes using scissors. Twelve grams of sulfonamide powder were added to the gel cubes and the mixture was warmed for 20 min in a water bath at 55—60 °C with stirring at 200 rpm, then poured into 300 g of liquid paraffin previously heated to about 55—60 °C. The mixture was stirred for 5 min at 200 rpm, then the glass vessel was placed in ice water, and cooled quickly to less than 5 °C. Stirring at 300 rpm was continued for 90 min and the temperature was kept at 5 °C until the gelatin microdrops had gelatinized completely. Dehydration was carried out by adding 150 g of isopropanol (temperature about 5 °C) and the solution containing the gelatinized gelatin microdrops was stirred at 300 rpm for 30 min. The gelatin microcapsules were separated by filtration, washed three times with 60 g of isopropanol at 5 °C and dried until the odor of isopropanol was indetectable by exposure to air from a dryer at low temperature. Sustained-release microcapsules were obtained by immersing 1 g of microcapsules in 10 ml of 10% formalin–isopropanol in a covered glass vessel, followed by hardening in a refrigerator at 2—5 °C for 24 h, and drying.

Dissolution Test——The *in vitro* release properties of the capsules prepared as described above were evaluated in a commercial rotating-bottle apparatus (Toyama Sangyo Co., TR-3S type) according to the procedures described in USP XIX and NF XIV. The blade, attached to the stirring motor by means of a steel shaft, was centered at a height of 3 cm from the bottom of the dissolution beaker. Five hundred ml of the dissolution medium (J.P. No.1 solution, pH 1.2, used in the J.P. "disintegration test") was introduced into the beaker and the stirring motor was turned on at a speed of 50 rpm for sulfanilamide and sulfisomidine and 100 rpm for sulfamethizole. An accurately weighed amount corresponding to 250 mg as sulfonamide (powder or microcapsules) was gently spread over the surface of the dissolution mediun, which was maintained at 37 °C. At appropriate intervals, 2 ml samples were withdrawn by means of a pipette. The pipette was fitted with a short piece of plastic tubing filled with a small piece of cotton to filter off any solid drug particles. The

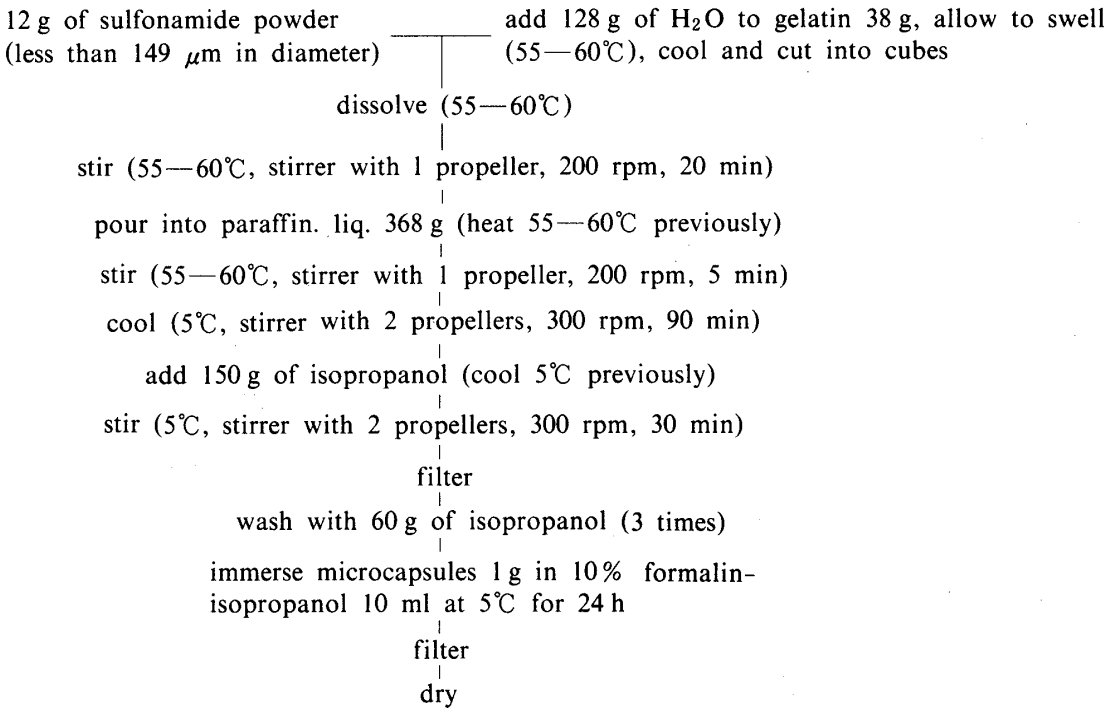


Chart 1. Preparation of Gelatin Microcapsules

sample volume taken was replaced by an equivalent volume (2 ml) of fresh dissolution medium and the volume of dissolution medium in the beaker was kept constant (500 ml). The release results were plotted as percentages of sulfonamide extracted into the dissolution medium from the microcapsules *vs.* time.

Analysis of Samples———Samples were diluted appropriately with water. Sulfonamides were diazotized in the regular manner,[5,6] with 0.1 % Tsuda reagent. The concentration was established spectrophotometrically by using the 540 nm band for sulfanilamide, the 538 nm band for sulfisomidine, and the 542 nm band for sulfamethizole.

Sulfonamide Content———A 30 mg sample was accurately weighed. Then about 40 ml of 5 % HCl was added, and the suspension was allowed to stand at 55—60°C for about 60 h. The microcapsules were thereby ruptured, and the drug dissolved. The solution was accurately diluted with water (5—10 times), and sulfonamides were assayed spectrophotometrically as described in the previous section. All samples were analyzed in duplicate.

Solubility of Sulfonamides———A 3 g sample of drug powder was accurately weighed into a 20 ml ampule and 10 ml of water was added. The ampule was sealed, placed in a constant temperature (37 or 55°C) bath and allowed to stand for several days. An equilibrated concentration of sulfonamides was established and was measured by using the analytical method described in the above section.

Particle-size Analysis———An electromagnetic vibration sieve (Micro-1 type, Tsutsui Rikagaku Kikai Co.) was used for this analysis. The particle-size distribution of the dried particles (5 g) was determined with 9, 16, 20, 24, 32, 42 and 60 mesh sieves (2000, 1000, 840, 710, 500, 350 and 250 μm in diameter). After vibration for 20 min, the portions collected on each screen were weighed accurately and a frequency distribution chart was made. All samples prepared on separate days were analyzed in duplicate.

The following abbreviations are used: SA for sulfanilamide, SI for sulfisomidine and SM for sulfamethizole.

Results and Discussion

Reproducibility of Microcapsule Preparation

Microcapsules with a particle size of 250—840 μm accounted for about 80 percent of the total product prepared by this microencapsulation procedure. Figure 1 shows a photomicrograph of microcapsules containing sulfamethizole in the form of a free-flowing powder.

These particles are essentially polynuclear microcapsules containing sulfonamide particles. The weight percent of microcapsule particles lying within a certain size range is plotted against size range in Fig. 2. Reproducible frequency distribution data for sulfisomidine microcapsules are shown in Fig. 2 as a typical example. The other two sulfonamides gave similar results. The two distributions were obtained from different lots of microcapsules prepared on separate days. The microcapsules with a diameter of 250—840 μm were used in absorption experiments with rabbits.

Recovery of Sulfonamides in Microcapsules

Table I summarizes the physical and pharmacokinetic parameters of sulfonamides used in this study.

The preparation of microcapsules was done with four different weight percent levels of sulfonamides. The amounts of sulfonamides embedded in the final products were determined by extracting the microcapsules with 5% HCl for 60 h at 60°C. The recovery of sulfonamides from any given lot was almost complete, as shown in Table II.

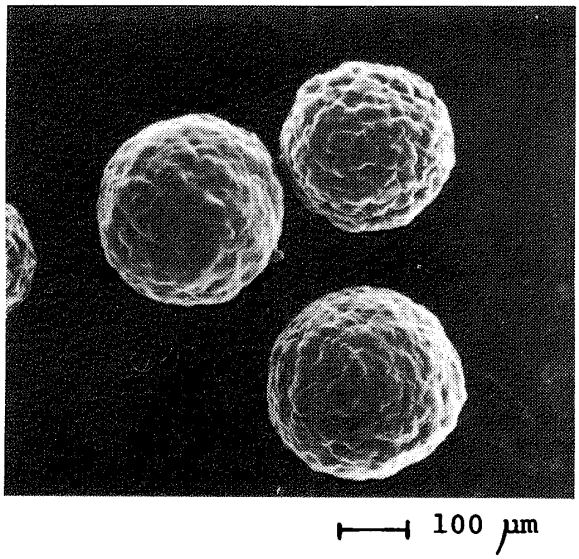


Fig. 1. Photomicrograph of Microcapsules containing 20% (w/w) Sulfamethizole as Discrete Particles

***In Vitro* Release of Sulfonamides from Microcapsules**

The apparatus used for the dissolution test is shown in Fig. 3. The release characteristics of the microcapsules are represented in Figs. 4—6 for SA, SI and SM, respectively.

The effect of the concentration of formalin in isopropanol on the hardening of microcapsules and on the *in vitro* release of sulfonamides from microcapsules was also examined. The results indicate that the dissolution pattern did not change in the region of 10—20% (v/v), and thus 10% formalin-isopropanol solution and an immersion time of 24 h were selected as the

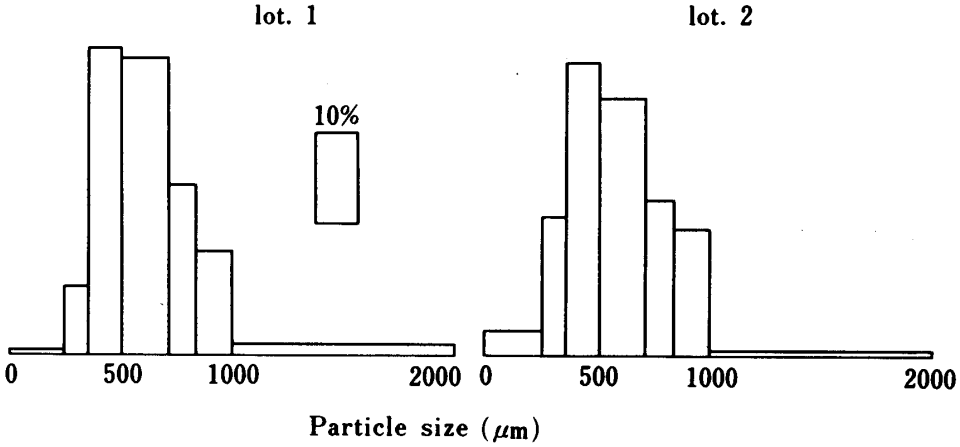


Fig. 2. Reproducibility of Frequency Distribution Data for Microcapsules containing 20% (w/w) Sulfisomidine

Two distributions are shown; lots 1 and 2 were obtained from different products prepared on separate days.

TABLE I. Physical and Pharmacokinetic Parameters of Sulfonamides used in This Study

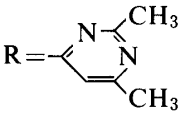
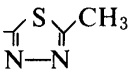
Sulfonamide	H_2N-⟨⟩-SO_2NH-R	mp	Solubility in H_2O (g/l)	pK_{a1}	pK_{a2}	$t_{0.5}$ (h, in man)
Sulfanilamide (SA)	R=-H	163—166℃	17.10 (37℃) 39.86 (55℃)	2.36	10.43	8.8
Sulfisomidine (SI)	R= 	245—249℃ (dec.)	1.88 (37℃) 3.35 (55℃)	2.36	7.7	7.4
Sulfamethizole (SM)	R= 	207—211℃	0.87 (37℃) 2.10 (55℃)	2.00	5.45	1.6

TABLE II. Components used for Preparation of Microencapsulated Sulfonamides and Drug Recoveries

Sample[a]	Components for preparation (g)		Recovery percent (w/w)[b]		
	Gelatin	Sulfonamide	SA[c]	SI[c]	SM[c]
MC-10	43	7	8.6	11.4	11.5
MC-20	38	12	19.9	20.8	18.2
MC-30	33	17	28.4	29.6	26.1
MC-40	30	20	34.9	37.9	40.7

a) For instance, MC-10 represents gelatin microcapsules containing about 10% (w/w) sulfonamide.
b) These values are averages of two or three experiments.
c) SA, sulfanilamide; SI, sulfisomidine; SM, sulfamethizole.

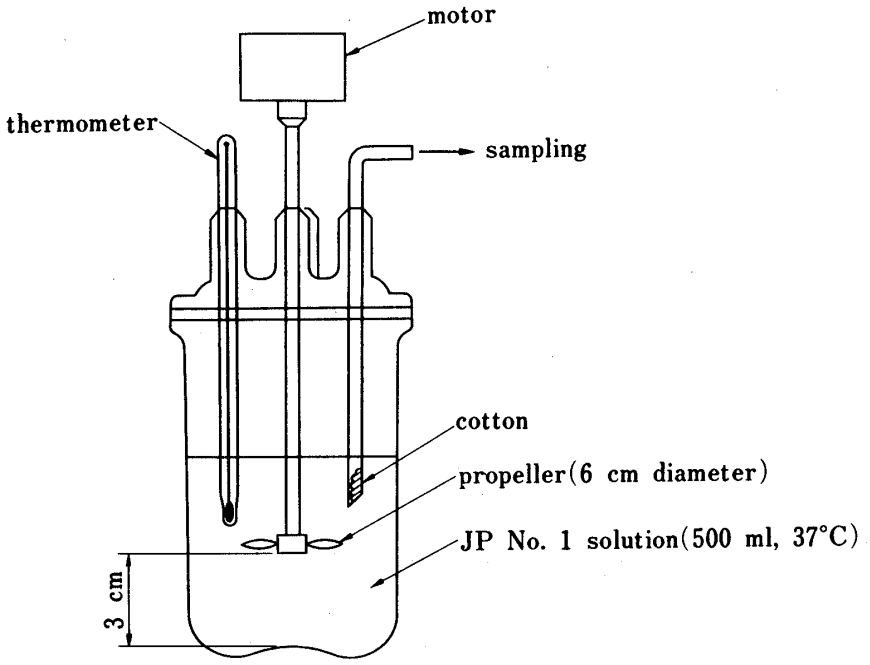


Fig. 3. Apparatus for the Dissolution Test

standard conditions for hardening. A close agreement between the dissolution patterns of the powder and microcapsules which had not been treated with 10% formalin–isopropanol solution (untreated microcapsules) was obtained.

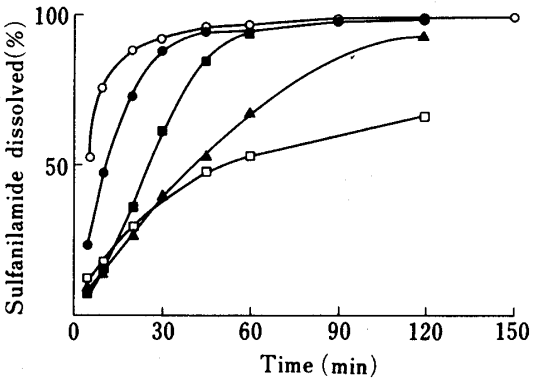


Fig. 4. Dissolution Pattern of Sulfanilamide (SA) from Powder and Microcapsules at 37°C, pH 1.2 and 50 rpm

○, SA powder; ●, MC-SA-40; ■, MC-SA-30; ▲, MC-SA-20; □, MC-SA-10.

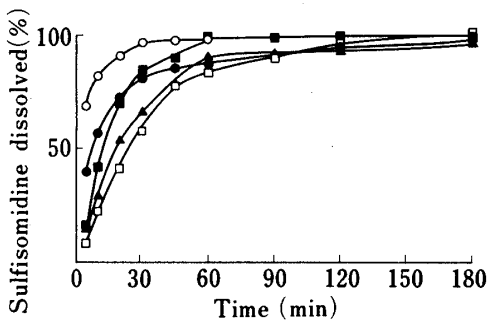


Fig. 5. Dissolution Pattern of Sulfisomidine (SI) from Powder and Microcapsules at 37°C, pH 1.2 and 50 rpm

○, SI powder; ●, MC-SI-40; ■, MC-SI-30; ▲, MC-SI-20; □, MC-SI-10.

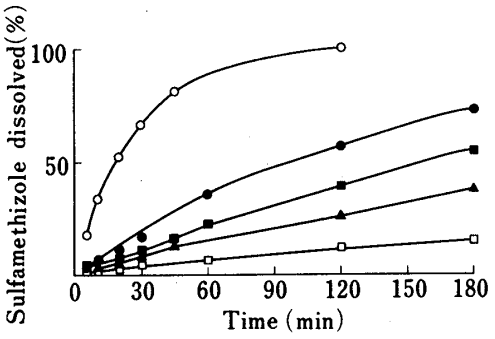


Fig. 6. Dissolution Pattern of Sulfamethizole (SM) from Powder and Microcapsules at 37°C, pH 1.2 and 100 rpm

○, SM powder; ●, MC-SM-40; ■, MC-SM-30; ▲, MC-SM-20; □, MC-SM-10.

Figures 4—6 show that the encapsulation process produced microcapsules which provided controlled release of sulfonamides, particularly in the case of SM. Powder particles of SA and SI dissolved completely in less than 60 min but it took more than 120 min for complete drug release from the treated microcapsules containing 10 and 20% (w/w) of these drugs.

On the other hand, SM powder dissolved slowly and hardening of the microcapsule wall slowed the drug release significantly. Moreover, the time required for complete drug release increased as the SM content of the microcapsules decreased. One of the aims of microencapsulation is to obtain zero-order drug release from the microcapsules. Unfortunately, experience shows that most microcapsule formulations release the drug at roughly a first-order rather than a zero-order rate. Figure 6 shows roughly zero-order kinetics for microcapsules containing 10 and 20% (w/w) sulfamethizole from 0 to about 10 or 30% dissolution.

Duplicate batches of microcapsules prepared at various times were almost identical to the first batch in terms of batch yield, microcapsule size distribution, and release rate profile. Further work is necessary to analyze the *in vitro* release rate profiles of the other two sulfonamides (SA and SI). The process described here is a quite simple and economical method and should be useful as a first step in the development of clinically useful sustained-release preparations. The *in vivo* application of these microcapsules in rabbits will be reported in subsequent papers.

References and Notes

1) *a*) This paper forms part VI of a series entitled "Evaluation of Microcapsules"; *b*) The preceding paper, part V: S. Goto, T. Tanaka and M. Kawata, *Yakuzaigaku,* **42**, 238 (1982).
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