

## Usefulness of the Final Filter of the IV Infusion Set in Intravenous Administration of Drugs —Contamination of Injection Preparations by Insoluble Microparticles and Its Causes—

Keiji KURAMOTO,<sup>\*,a</sup> Toru SHOJI,<sup>b</sup> and Yoshito NAKAGAWA<sup>c</sup>

<sup>a</sup>Pharmacy Section, Medical Corporation Funayama Hospital, 2–4–8 Ekimae, Yonezawa City 992–0027, Japan,

<sup>b</sup>Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Ohu University, 31–1 Sankakudou, Tomitamachi, Kooriyama City 963–8611, Japan, and <sup>c</sup>Pharmacy Department, Yamagata University Hospital, 2–2–2 Nishiida, Yamagata City 990–9585, Japan

(Received October 19, 2005; Accepted January 27, 2006)

The purpose of this study is to clarify the presence of so much insoluble microparticles in the injections and to confirm the usefulness of the final filter for its removal. The test drugs used were Doyle<sup>®</sup> 1 g vial, Cefotax<sup>®</sup> 1 g vial, Minomycin<sup>®</sup> 100 mg vial, Omegacin<sup>®</sup> 0.3 g vial, Maxipime<sup>®</sup> 1 g vial, Rocephin<sup>®</sup> 1 g vial, Isovorin<sup>®</sup> 25 mg vial, Diamox<sup>®</sup> 500 mg vial and Fungizone<sup>®</sup> 50 mg vial. 1) An appropriate volume of physiological saline was poured into the test drug vial from the 500 ml physiological saline bag. 2) The dissolution of the preparation was checked. 3) That test drug solution was returned into the same 500 ml physiological saline bag. 4) 5 ml of test drug solution was extracted from the inside of the 500 ml physiological saline bag. 5) The number of insoluble microparticles in the each test drug solution at pre- and post-filtrations were counted by using a particle counter for the solution. Two results were shown as follows (microparticle size: 5  $\mu$ m or greater), (a) Doyle<sup>®</sup> 1 g (ASPC): The number of insoluble microparticles in pre- and post-filtrations of a Doyle<sup>®</sup> 1 g vial were  $250 \pm 45$  and 0/5 ml, respectively (microparticle size:  $\leq 5 \mu$ m 1662/5 ml, 5–10  $\mu$ m: 238/5 ml,  $> 10 \mu$ m: 11/5 ml). (b) Diamox<sup>®</sup> 500 mg (acetazolamide): The number of insoluble microparticles in pre- and post-filtrations of Diamox<sup>®</sup> were  $158 \pm 53$  and  $0.3 \pm 0.47/5$  ml, respectively (microparticle size:  $\leq 5 \mu$ m 4030/5 ml, 5–10  $\mu$ m: 144/5 ml,  $> 10 \mu$ m: 14/5 ml). The presence of great numbers of insoluble microparticles in several injection preparations was clarified. Although the all test drugs used cleared the criteria of the number of insoluble microparticles of the Japanese Pharmacopoeia, it was suggested to be not suitable that great numbers of insoluble microparticles were administered in the body fluid of patients, because a possibility to occlude capillaries and/or to injure the tissues by them was been thought. But we could remove them nearly completely by passing the solutions of drugs through an infusion filter. Otherwise, in this examination, we found that so much insoluble microparticles derived from the disposable syringe (10 ml) were used for dissolving freeze-dried preparations routinely (microparticle size:  $\leq 5 \mu$ m 329/5 ml, 5–10  $\mu$ m: 125/5 ml,  $> 10 \mu$ m: 39/5 ml). These results suggest that incorporation of a final filter in the IV line is extremely necessary not only for the prevention of bacterial infections, but also for elimination of insoluble microparticles.

**Key words**—microparticles; removal; filter; freeze-dried preparation; contamination

### INTRODUCTION

Insoluble microparticles are occasionally detected in injection preparations. Although the 14th edition of the Japanese Pharmacopoeia determines tolerable ranges of the number of insoluble particles contained in injection preparations for quality control,<sup>1)</sup> these tolerable ranges have not been sufficiently validated. There have been few studies that evaluated such insoluble microparticles in Japan,<sup>2)</sup> and their effects on the body in the administration of large doses of drugs remain uncertain.<sup>3)</sup> Therefore, we measured the number of insoluble microparticles contained in solutions of freeze-dried injection preparations to clarify the

contents of microparticles in drugs of common clinical use and demonstrated that an infusion filter is useful for their removal.

### MATERIALS AND METHODS

First, to select the infusion preparation with which lyophilized preparations would be dissolved, the number of insoluble microparticles was examined in a 100-ml polypropylene (PP) bag of physiologic saline and a 500-ml ethylene-vinyl acetate (EVAC) bag of physiologic saline (Terumo), which were available in this study.

Next, as shown in Table 1, test solutions were prepared by dissolving 18 freeze-dried preparations of 6 antibiotics and 1 each of an anticancer agent, an antifungal agent, and a diuretic with different manufac-

\*e-mail: phm\_f@yahoo.co.jp

Table 1. Test Drug Preparations

Name						
Freeze-dried preparation	Ingredient	Company	Classification		Lot. No.	
Cefotax <sup>®</sup> 1 g	Cefotaxime sodium	CHUGAI	Antibiotics	A3H60	A3H60	A4F60
Minomycin <sup>®</sup> 100 mg	Minocycline hydrochloride	Wyeth-TAKEDA	Antibiotics	174-1	174-1	251-1
Omegacin <sup>®</sup> 0.3 g	Biapenem	Wyeth-MEIJII	Antibiotics	1621	1631	1731
Maxipime <sup>®</sup> 1 g	Cefepime dihydrochloride	BMS	Antibiotics	MXV380	MXV260	MXVB850
Doyle <sup>®</sup> 1 g	Aspoxillin	TANABE	Antibiotics	45001	45001	48003
Rocephin <sup>®</sup> 1 g	Ceftriaxone sodium	Roche	Antibiotics	K125451	K127461	K1424Z1
Isovorin <sup>®</sup> 25 mg	Levofolinate calcium	Wyeth-TAKEDA	Anticancer agent	547-1	554-1	595-1
Fungizone <sup>®</sup> 50 mg	Amphotericin B	BMS	Antifungal agent	FZV2232	FZV2251	FZV2301
Diamox <sup>®</sup> 500 mg	Acetazolamide	Wyeth-TAKEDA	Diuretics	304-1	304-1	DK110F

Test solutions were prepared by dissolving 27 freeze-dried preparations with different manufacturer's serial numbers. Each solution was collected 3 times, insoluble microparticles were counted.

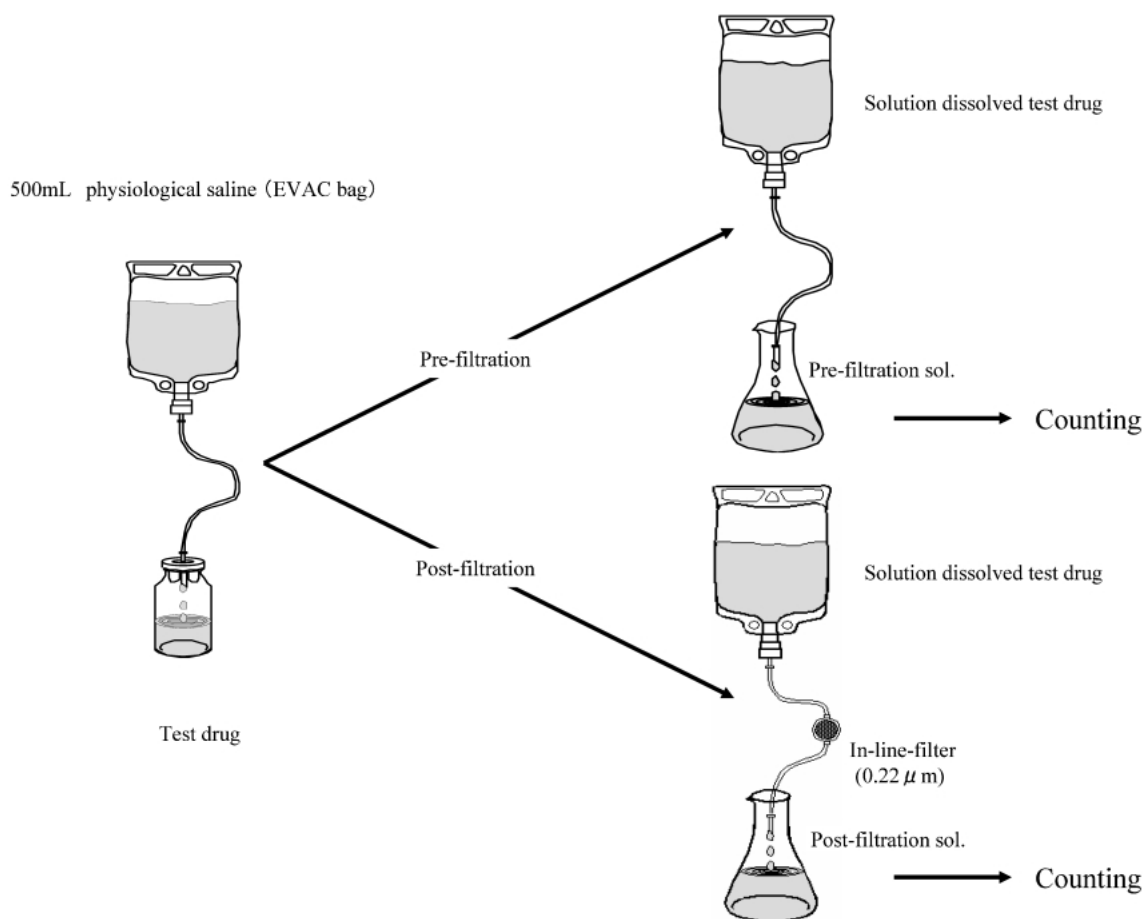


Fig. 1. Methods of Preparing Each Test Solution

The freeze-dried preparations were dissolved by connecting a bag containing 500 ml of physiological saline with a vial containing a test preparation using a tube washed with water for injection, infusing an appropriate volume of it, and returning it to the infusion bag after confirmation of sufficient dissolution of the drug. From the 500-ml bag of physiological saline containing a dissolved test drug, 100 ml was collected in a conical flask as sample solution (1). Sample solution (2) was collected through an infusion filter (0.22 μm).

turer's serial numbers with 500 ml of physiological saline (Terumo). As shown in Fig. 1, the freeze-dried preparations were dissolved by connecting a bag

(ethylene-vinyl acetate; EVAC) containing 500 ml of physiological saline with a vial containing a test preparation using a tube washed with water for injec-

tion prepared by ultrafiltration (experimental water), infusing an appropriate volume of physiological saline, and returning the saline to the infusion bag after confirmation of sufficient dissolution of the drug. From the 500-ml bag of physiological saline containing a dissolved test drug, 100 ml was collected in a conical flask as sample solution (1). Sample solution (2) was collected through an infusion filter (0.22  $\mu\text{m}$ ). Five milliliters of sample solutions (1) and (2) were collected 3 times, insoluble microparticles were counted, and the mean value was calculated for each solution. The number and size of insoluble microparticles were determined using a Model 8000 A automatic microparticle analyzer for liquids<sup>®</sup> (Hiac/Royco), which conformed to the method using a light-shielded type automatic microparticle counter prescribed by the Japanese Pharmacopoeia. Two lots of each drug were examined. The physiological saline was used after filtration with an infusion filter (0.22  $\mu\text{m}$ ). The conical flasks were used after they were washed with experimental water until no insoluble microparticles became observable. All procedures were carried out in a clean bench. The tube used to connect the infusion bag with the drug vial was Terufusion<sup>®</sup> tube TC-00503 K (Terumo). The infusion filter was Terufusion<sup>®</sup> Final Filter PS TF-SW231H (Terumo) with a pore size of 0.22  $\mu\text{m}$ . The infusion set was TS-PA200L (Terumo) for the Terufusion<sup>®</sup> pump. We also evaluated the number of insoluble microparticles derived from Terumo SS-10LZ 10-ml syringes (Terumo), which were disposable syringes routinely used for dissolving freeze-dried preparations in clinical practice.

## RESULTS

### Microparticles Derived from the Devices Used

The mean number of insoluble microparticles 5  $\mu\text{m}$  or greater in 100-ml bags of physiological saline (Terumo; made of polypropylene (PP)), which is routinely used for dissolving freeze-dried preparations, was  $12 \pm 3.3/5$  ml. The mean number of insoluble microparticles 5  $\mu\text{m}$  or greater in 500-ml EVAC bags of physiological saline was  $1 \pm 0.5/5$  ml. Next, the number of insoluble microparticles derived from disposable syringes routinely used for dissolving freeze-dried preparations was determined by aspirating 10 ml of saline with a 10-ml disposable syringe from a 100-ml bag (PP) of physiological saline, returning it to the same bag, and counting insoluble microparticles in

the bag. The mean number of insoluble microparticles 5  $\mu\text{m}$  or greater was  $164 \pm 1.4/5$  ml. Therefore, we dissolved freeze-dried preparations by connecting a 500-ml bag of physiological saline with a drug vial using a tube and counted insoluble microparticles in the solutions prepared by this method. As a result, the number of insoluble microparticles 5  $\mu\text{m}$  or greater was  $22 \pm 5.9/5$  ml. However, when the tube that connected the saline bag and the drug vial was washed once with 20 ml of experimental water, no insoluble microparticle 5  $\mu\text{m}$  or greater was observed in the solutions.

### Number of Insoluble Microparticles in Freeze-dried Preparations

Figure 2 shows the numbers of insoluble microparticles 5  $\mu\text{m}$  or greater contained in 5 ml of 27 preparations of 9 freeze-dried drugs. The mean number of insoluble microparticles was largest at  $250 \pm 45/5$  ml in Doyle<sup>®</sup> (ASPC), followed by  $158 \pm 53/5$  ml in Diamox<sup>®</sup> (acetazolamide) and  $129 \pm 29/5$  ml in Fungizone<sup>®</sup> (AMPH). These values are equivalent to 25000, 15800, and 12900 per 500 ml. Among the lowest values were  $18 \pm 17/5$  ml in Rocephin<sup>®</sup> (CTRX) and  $11 \pm 5/5$  ml in Isovorin<sup>®</sup> (levofolinate Ca). Still, these values are equivalent to 1800 and 1100 per 500 ml. The 6 antibiotics ranked in the number of insoluble microparticles in the order of ASPC > CFPM > BIPM  $\approx$  CTRX > MINO  $\approx$  CTRX.

### Ability of the Infusion Filter to Remove Insoluble Microparticles

The number of insoluble microparticles 5  $\mu\text{m}$  or greater in 5 ml of the solutions of the 27 preparations of 9 test drugs was 0–2/5 ml after they were passed through the infusion filter, indicating nearly complete elimination. When insoluble microparticles 2  $\mu\text{m}$  or greater were counted, they were also removed by the infusion filter. Figure 3 shows an example with Rocephin<sup>®</sup> (CTRX). Although the number of insoluble microparticles 5  $\mu\text{m}$  or greater was smallest in Rocephin<sup>®</sup> (CTRX) among all the freeze-dried preparations examined in this study, it contained many insoluble microparticles 2  $\mu\text{m}$  or greater, most of which were also removed by an infusion filter (elimination rate: 95.6%).

## DISCUSSION

The Japanese Pharmacopoeia requires tests of insoluble microparticles in all injection preparations.<sup>1)</sup> According to the handbook for the 14th edition of the Japanese Pharmacopoeia (2001), the criteria of the number of insoluble microparticles are as follows:

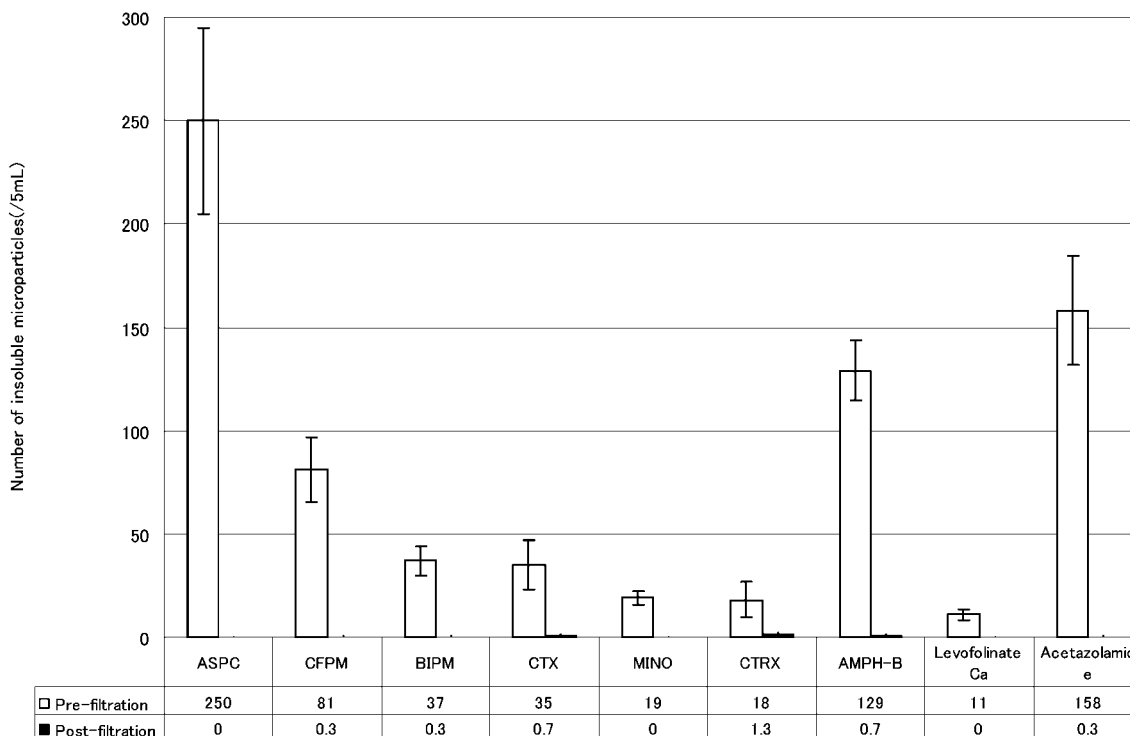


Fig. 2. Number of Insoluble Microparticles in Solutions of Freeze-dried Pharmaceutical Preparations (Microparticle Size  $\geq 5 \mu\text{m}$ )  $n = 3$ , mean  $\pm$  S.D.

Each sample was collected 3 times, insoluble particles were counted, and the mean value was calculated.

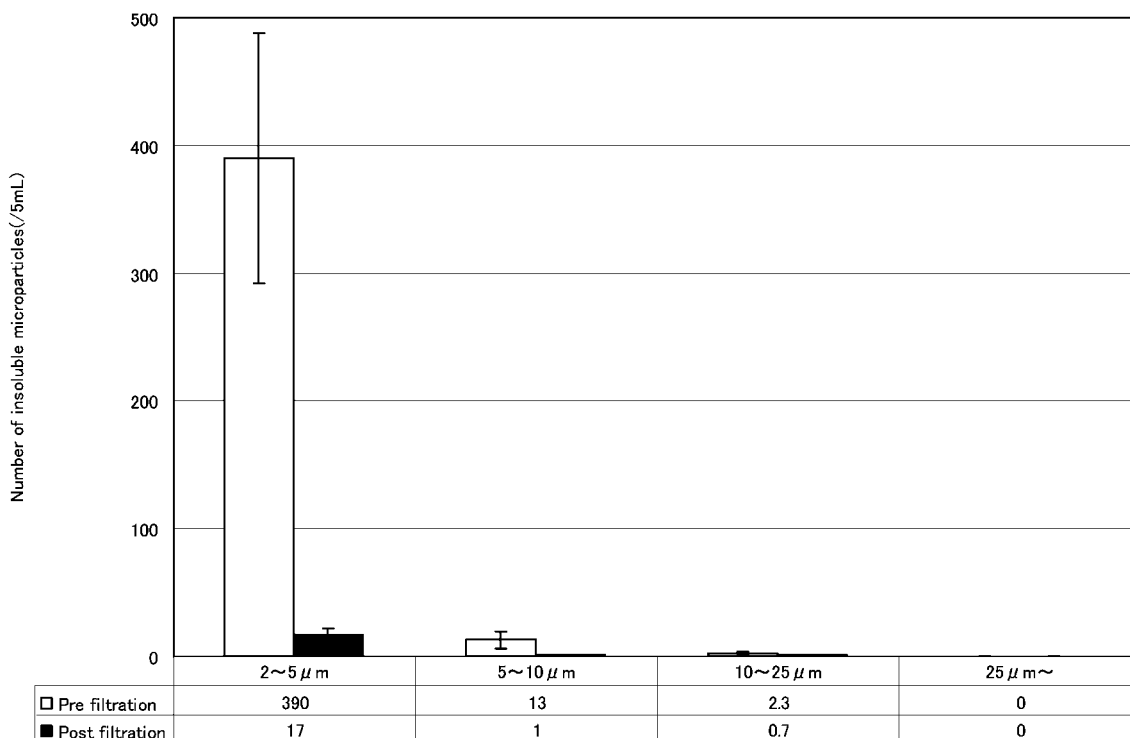


Fig. 3. Comparison with Pre- and Post-filtration of Number of Insoluble Microparticles in the Solution of Rocephin® 1 g Vial (Microparticle Size  $\geq 2 \mu\text{m}$ )  $n = 3$ , mean  $\pm$  S.D.

Rocephin® (CTRX) had the smallest number of insoluble microparticles  $5 \mu\text{m}$  or greater among the all samples. But it contained many insoluble microparticles  $2 \mu\text{m}$  or greater.

Table 2. Criteria of Japanese Pharmacopoeia (Insoluble Microparticles)  
Method 1: Light-shielded Type Automatic Microparticle Counter

Volume of preparation	Microparticle size	Criteria value
less than 100 ml	10 $\mu\text{m}$ or greater	6000/container or less
	25 $\mu\text{m}$ or greater	600/container or less
100 ml or more	10 $\mu\text{m}$ or greater	25/ml or less
	25 $\mu\text{m}$ or greater	3/ml or less

Method 2: Microscope		
Volume of preparation	Microparticle size	Criteria value
less than 100 ml	10 $\mu\text{m}$ or greater	3000/container or less
	25 $\mu\text{m}$ or greater	300/container or less
100 ml or more	10 $\mu\text{m}$ or greater	12/ml or less
	25 $\mu\text{m}$ or greater	2/ml or less

As shown in Table 2, the Japanese Pharmacopoeia requires criteria for insoluble microparticles.

For injection preparations administered at 100 ml or more, the tolerated number of insoluble microparticles 10  $\mu\text{m}$  or greater is 25 or less, and that of particles 25  $\mu\text{m}$  or greater is 3 or less, per 1 ml. For injection preparations administered at less than 100 ml, the tolerated number of insoluble microparticles 10  $\mu\text{m}$  or greater is 6000 or less, and that of particles 25  $\mu\text{m}$  or greater is 600 or less, per container (method using a light-shielded type automatic microparticle counter) (Table 2). However, no permissible range is shown concerning microparticles 10  $\mu\text{m}$  or smaller. Although effects of microparticles on the body are not clear, intravenous injection of unnecessary materials should be avoided. Accidents due to incompatibility of calcium phosphate<sup>4)</sup> and death due to pulmonary embolism by glass fragments considered to be derived from cutting of ampoules<sup>5)</sup> have been reported. The British Pharmaceutical Nutrition Group Working Party (BPNG) has issued a guideline from a viewpoint of avoiding stressing human bodies with insoluble microparticles.<sup>6)</sup> In these circumstances, the National Coordinating Committee on Large Volume Parenterals (NCCLVP), Intravenous Nurses Society (INS), and Food and Drug Administration (FDA) of the United States have recommended incorporation of a final filter in the IV line for intravenous administration of drugs. In Japan, also, there are guidelines requiring incorporation of a final filter in the IV line.<sup>7-9)</sup> However, the guideline of the Centers for Disease Control and Prevention (CDC)<sup>10)</sup> does not

explicitly acknowledge the significance of the final filter. It must be remembered that this recommendation was issued in the medical background of the United States, where preparations for Total Parenteral Nutrition (TPN) are provided to clinical departments after removing bacteria, foreign bodies, and insoluble microparticles at the pharmacy. An infusion filter is considered to be absolutely necessary in Japan, where TPN fluids are prepared in the ward or are mixed with many other drugs via a 3-way stopper. While a final filter is considered to be useful for elimination of insoluble microparticles in Japan, data that support this view have not been reported after Uchida et al. in 1979.<sup>11)</sup> We, therefore, clarified the presence of insoluble microparticles in injection preparations and evaluated the usefulness of an infusion filter for its removal.

First, since insoluble microparticles derived from the devices must be eliminated, conditions for their elimination were evaluated. As mentioned above, we carried out experiments by completely eliminating insoluble microparticles derived from instruments. Also, our experiment indicated that 500-ml bags (made of EVAC) of physiological saline used for dissolving drugs contain very few insoluble microparticles 5  $\mu\text{m}$  or greater. We consider that insoluble microparticles other than those contained in the drugs could be completely eliminated in this study by: 1) not using disposable syringes and connecting the saline bag and drug vial with a tube washed with ex-

perimental water, 2) using instruments for the collection of sample solutions after washing them with experimental water, and 3) selecting infusion vehicles used for dissolving drugs from those with minimum contents of insoluble microparticles.

Concerning the number of insoluble microparticles derived from the devices used, the mean value was  $12 \pm 3.3$  particles/5 ml in the 100-ml PP bag of physiologic saline and was higher than the value for the 500-ml EVAC bag of physiologic saline (1 particle/5 ml). Also, the number of insoluble microparticles was the smallest in the 500-ml EVAC bag of physiologic saline among all the infusion preparations examined in this study. Therefore, we used a 500-ml EVAC bag of physiologic saline to dissolve the lyophilized preparations, although this combination is unlikely in clinical practice. The objective of this selection was to minimize the effect of insoluble microparticles in the infusion preparation and to exclusively evaluate insoluble microparticles contained in drugs. The differences in the number of insoluble microparticles observed in this study were caused by differences in the manufacturing line in the factory rather than differences in the bag material. Also, among the mean numbers of insoluble microparticles derived from the devices used for the dissolution of lyophilized preparations, that observed after the manipulation of the 10-ml disposable syringe was high at  $164 \pm 1.4/5$  ml. This time, the identification of these insoluble microparticles was not done. However, we guess that a lot of TPE (Thermoplastic Elastomers), silicon oil and the others were included in them. Therefore, it was not used in this study. Moreover, to eliminate the small number of insoluble microparticles derived from devices, the connecting tube was used after washing it with water for injection prepared by ultrafiltration to remove all insoluble microparticles.

Concerning the numbers of insoluble microparticles in the lyophilized preparations, a wide variation was observed, but all samples contained many insoluble microparticles derived from the preparations (Fig. 2). Since the sample volume was 5 ml, the total number of insoluble microparticles derived from preparations was estimated to be as high as 25000 in ASPC, 8100 in CFPM, and 3700 in BIPM, and to be 1800 even in CTRX, which contained the smallest number of insoluble microparticles among the 6 antibiotics. Also, if the preparations had been dissolved with a 100-ml bag of physiologic saline, even greater

numbers of insoluble microparticles might have resulted. This means that contamination by insoluble microparticles may be aggravated if drugs including lyophilized preparations are mixed in a single infusion preparation. While these values are surprisingly high, they still meet the criteria of the Japanese Pharmacopoeia concerning insoluble microparticles, which are not softer than those of foreign pharmacopoeias. However, in consideration of the situation in Japan whereby multiple drugs are more often mixed in a single infusion preparation for administration than in foreign countries, a stricter revision of the Japanese Pharmacopoeia may be necessary.

Concerning the ability of the infusion filter to eliminate insoluble microparticles, it almost completely removed those derived from lyophilized preparations, as was expected. In CTRX, for example, the elimination rate was 95.6%. These results confirmed that the use of an infusion filter is effective for the elimination of insoluble microparticles derived from preparations contaminating infusion preparations.

In this study, insoluble microparticles  $5 \mu\text{m}$  or greater were evaluated, because there have been reports that particles of this size may obstruct arterioles and capillaries.<sup>12,13)</sup> Also, it became clear that insoluble microparticles less than  $5 \mu\text{m}$  are contained in greater numbers. Although whether these insoluble microparticles were undissolved components of drugs or foreign bodies that entered in the manufacturing process was not determined, they were shown to be eliminated nearly completely by passing the solutions of drugs through an infusion filter. These results suggest that incorporation of a final filter in the IV line is necessary not only for the prevention of bacterial infections but also for elimination of insoluble microparticles. The Japanese Pharmacopoeia prescribes the criteria for insoluble microparticles  $10 \mu\text{m}$  or greater and those  $25 \mu\text{m}$  or greater, but the special report of the ASPEN<sup>12)</sup> recommends attention to particles  $5 \mu\text{m}$  or greater. In addition, the number of insoluble microparticles may increase if the drug has been dissolved with 100 ml of a vehicle. We, therefore, demand a revision of the Japanese Pharmacopoeia concerning the testing methods for insoluble microparticles. In the present state, however, we propose the incorporation of a final filter into the IV line in intravenous administration of drugs to eliminate insoluble microparticles derived from drugs, manufacturing processes, and devices such as

the disposable syringe, regardless of the quantity of administration.

### CONCLUSION

These results suggest that incorporation of a final filter in the IV line is extremely necessary not only for the prevention of bacterial infections, but also for elimination of insoluble microparticles.

### REFERENCES

- 1) "The 14th edition of the Japanese Pharmacopoeia, Instruction manual," Hirokawa Book Co., Tokyo, 2001, p. A-78-92
- 2) Horioka M., Aoyama T., Uchida K., *Jpn. J. Pharma. Sci. Technol.*, **33** (4), 191-199 (1973).
- 3) Horioka M., *Jpn. J. Med. Instrument.*, **46** (11), 495 (1976).
- 4) FDA SAFETY ALERT: Hazards of Precipitation Associated with Parenteral Nutrition, April 18, 1994.
- 5) Ball P. A., *Jpn. J. Intrav. Ent. Feed.*, **16** (2), 113-121 (2001).
- 6) Bethune K., Allwood M., Granger C., Wormleighton C., *Nutrition*, **17**, 403-408 (2001).
- 7) Yamaguchi K., Takezawa J., Inoue Y., Ohta M., Sakakibara Y., Shoji T., Sugiura S., Tajimi K., Doi M., Nakagawa Y., Himeno M., Hirakata Y., Fukuoka T., "Medical device and environmental control for prevention of in-hospital infection in the 2nd Guideline of Catheter-related Blood Stream Infection Control," 2002, pp. 308-311 (Name of project: Research on Pharmaceutical and Medical Safety, Funding source: Health and Labour Sciences Research Grants, Ministry of Health, Labour and Welfare of Japan).
- 8) Infection Control Meeting of National University Hospitals, "Guideline for In-hospital Infection Control," 2002, pp. 97-127.
- 9) Meeting on CV Catheter or Device, "Guideline for Standardization of CV Catheter Management," 2002, p. 10.
- 10) CDC, "Guideline for the Prevention of Intravascular Catheter-Related Infections," 2001, pp. 15-16.
- 11) Uchida K., Aoyama T., Akashi S., Horioka M., *Jpn. J. Pharma. Sci. Technol.*, **36** (2), 55-63 (1976).
- 12) ASPEN, "National Advisory Group on Standards and Practice Guidelines for Parenteral Nutrition," 1997, p. 5.
- 13) Pump K. K., "Normal Lung Anatomy in Clinical Cardiopulmonary Physiology, Third ed.," 1969, p. 332.