Research Note

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Comparison of Particulate Contamination in Glass and Plastic Ampoules of Glycyrrhizin Injections after Ampoule Cutting

KATSUHIRO YORIOKA[1]*, SHIGEHARU OIE[2] AND AKIRA KAMIYA[2]

[1.] Department of Pharmacy, Shunan Municipal Shinnanyo Citizen Hospital, 2-3-15, Miyanomae, Shunan 746-0017, Japan
[2.] Department of Pharmacy, Yamaguchi University Hospital, 1-1-1, Minamikogushi, Ube 755-8505, Japan

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ABSTRACT

We evaluated the number and types of particles in glycyrrhizin injections after ampoule cutting. A total of 100 glass ampoules of 5 companies were examined. The mean number of particles with diameter of 1.3- < 5 μm was 252.9/mL, and that of particles with diameter of 5- < 10 μm was 12.5/mL. The number of particles differed among products of the 5 companies, e.g., the number of particles with a diameter of 1.3- < 5 μm varied from 351.9/mL to 121.6/mL. In addition, a total of 120 plastic ampoules from 6 companies were evaluated. The mean number of particles with a diameter of 1.3- < 5 μm was 43.0/mL, and that of particles with a diameter of 5- <10 μm was 2.1/mL. Differences among products of the 6 companies were not siqnificant. The number of particles in glycyrrhizin injections after ampoule cutting was significantly lower in plastic than for glass ampoules ($p < 0.0001$). Scanning electron microscopy and X-ray microanalysis identified glass fragments in glycyrrhizin injection samples after the cutting of glass ampoules but identified no particles after cutting plastic ampoules. Glycyrrhizin injections are commonly used in Asia including Japan, Taiwan, and China. The use of plastic ampoules is recommended for the prevention of the entry of glass fragments into the body.

Key words: particulate contamination, glycyrrhizin injection, glass ampoule, plastic ampoule, glass fragment

INTRODUCTION

Particles such as glass fragments in injections not only damage the brain, liver, and kidneys but also cause pulmonary embolism[1-8]. Therefore, the measures of specific contamination for injections are important, and so are the use of inline filters during intravenous drip infusion and membrane filters at the time of the preparation of drugs for injection. However, the use of inline filters or membrane filters is expensive and time-consuming. In many hospitals, inline filters are used only during total parenteral nutrition, and membrane filters are used only for the preparation of anticancer drugs in pharmacies. Thus, the measures of particulate contamination for injections are usually taken only at the time of total parenteral nutrition or the administration of anticancer drugs, while no measures are taken for drugs administered via a peripheral vein.

A commonly used injection is glycyrrhizin solution. Since glycyrrhizin injections are administered via a peripheral vein, inline filters are not currently used. In addition, the administration volume of this injection is 40-100 mL (2-5 ampoules), and long-term administration daily or 2-3 times/day is performed. When glass ampoules of glycyrrhizin injections are used, a large amount of glass fragments after ampoule cutting may enter the blood vessel. Therefore plastic ampoules of glycyrrhizin injections have become commercially available. However, since no studies have compared particles in this agent between glass and plastic ampoules, the usefulness of plastic ampoules has not yet been established. In this study, we compared particle contamination in glycyrrhizin injections between glass and plastic ampoules after ampoule cutting.

* Author for correspondence. Tel: +81-834-61-2500;
Fax: +81-834-61-2501; E-mail: yorioka-reywal@ric.hi-ho.ne.jp

MATERIALS AND METHODS

The numbers, diameters, and types of particles in glass ampoules 20 mL glycyrrhizin injections (n = 100) and plastic ampoules 20 mL glycyrrhizin (n=120) were evaluated (total, 220 samples). The glass ampoules were Stronger Neo-Minophagen® C (Company A, n = 20), Neophagen® C (Company B, n = 20), Glyveltin® (Compa-

ny C, n = 20), Kalosgen® (Company D, n = 20), and Kyominotin® (Company E, n = 20). The plastic ampoules were Stronger Neo-Minophagen® P (Company A, n = 20), Neophagen® (Company B, n = 20), Glyphagen C® (Company F, n = 20), Gulucolin S® (Company G, n = 20), Hishiphagen C® (Company H, n = 20), and Asphagen® (Company I, n = 20). Glycyrrhizin injections of the same lot of each pharmaceutical company were used. All glass ampoules were of the one-point cut type.

Samples were obtained by the following methods. Glass or plastic ampoules were cut and left for 3 minutes. Subsequently, a 10 mL injection sample was collected from the inside of the ampoule. These procedures were performed in a safety cabinet. The size and number of particles in samples after glass or plastic ampoules cutting were measured using a light blockage counter KL-04 (Rion K. K., Tokyo, Japan). Particles after ampoule cutting were counted using the first method (light blockage particle counting: light blockage counter KL-04) of the Foreign Insoluble Matter Test for Injection mentioned by the Pharmacopoeia of Japan, which was also used for particle counting in injections before ampoule cutting.

Glycyrrhizin solutions after ampoules cutting were filtrated through a 0.22 μm membrane filter (Nippon Becton Dickinson Co., Tokyo, Japan) in a safety cabinet. The particles on the membrane filter were observed and identified using a scanning electron microscope JSM-5600LV coupled to an energy dispersion spectroscope JEO-2200 (JMS, Tokyo, Japan). Statistical differences were analyzed by the Wilcoxon U-test.

RESULTS

Table 1 shows the mean (range) of particles in glycyrrhizin injection samples of a total of 100 glass ampoules (5 companies) and 120 plastic ampoules (6 companies). In the injection samples of glass ampoules, the number of particles with a diameter of 1.3- < 5 μm was 252.9/mL, that of particles with a diameter of 5- < 10 μm was 12.5/mL, that of particles with a diameter of 10- < 50 μm was 3.2/mL, and that of particles with a diameter of 50- < 100 μm was 0.09/mL. In injection samples of plastic ampoules, the mean number of particles with a diameter of 1.3- < 5 μm was 43.04/mL, that of particles with a diameter of 5- < 10 μm was 2.11/mL, that of particles with a diameter of 10- < 50 μm was 0.59/mL, and that of particles with a diameter of 50- < 100 μm was 0/mL. The number of particles was significantly higher

Table 1. The mean (range) of particles at each diameter in glycyrrhizin injections contained in glass and plastic ampoules

	Particle diameter (μm)			
	1.3 - < 5 μm	5 - < 10 μm	10 - < 50 μm	50 - 100 μm
Glass ampoule preparation				
Pharmaceutical company (A) (n=20)	293.4 (145-523)	12.45 (5-25)	3.8 (1-10)	0.15 (0-1)
Pharmaceutical company (B) (n=20)	166.15 (91-228)	5.45 (1-13)	1.3 (0-4)	0
Pharmaceutical company (C) (n=20)	331.65 (197-523)	17.75 (6-28)	3.95 (1-8)	0.15 (0-1)
Pharmaceutical company (D) (n=20)	121.6 (70-203)	5.55 (0-12)	1.95 (0-7)	0.05 (0-1)
Pharmaceutical company (E) (n=20)	351.95 (153-628)	21.65 (8-42)	5.05 (1-17)	0.1 (0-1)
Total (n = 100)	252.95*(70-628)	12.57*(0-42)	3.21*(0-17)	0.09 (0-1)
Plastic ampoule preparation				
Pharmaceutical company (A) (n=20)	57.95 (27-93)	1.55 (0-3)	0	0
Pharmaceutical company (B) (n=20)	44.45 (17-89)	1.7 (0-3)	0	0
Pharmaceutical company (F) (n=20)	39.75 (16-98)	2.3 (0-9)	1.05 (0-6)	0
Pharmaceutical company (G) (n=20)	45.7 (14-81)	3.55 (0-8)	1.45 (0-3)	0
Pharmaceutical company (H) (n=20)	36.2 (12-93)	1.75 (0-9)	0.5 (0-3)	0
Pharmaceutical company (I) (n=20)	34.2 (11-72)	1.8 (0-8)	0.55 (0-3)	0
Total (n = 120)	43.04 (11-98)	2.11 (0-9)	0.59 (0-6)	0

*$P < 0.0001$

in the injection samples of glass than in those of plastic ampoules ($p < 0.0001$).

Figure 1 shows scanning electron micrographs of three types of particles on the membrane filters after the filtration of glycyrrhizin injection samples following the cutting of glass ampoules and results of the identification of these particles by energy dispersion spectroscopy. Since X-ray analysis of particles on membrane filters showed a large amount of Si, these particles were identified as glass fragments. No particles were observed on membrane filters after the filtration of glycyrrhizin injection samples following the cutting of plastic ampoules.

DISCUSSION

One of the widely employed drugs for injection via peripheral veins is glycyrrhizin used for type C hepatitis. In general, glycyrrhizin for injection is administered as an intravenous injection or drip at a general dose of 40-100 mL (2-5 ampoules of 20 mL injection) once daily for the first 1 month and 2-3 times weekly for the subsequent 3 months or more. Thus, since glycyrrhizin for injection is administered at a large total dose for a long period, when glass ampoules are used for a long period, the risk of glass fragment accumulation in the body is high. Glycyrrhizin injection is used in more than 80% of Japanese hospitals, with about 52 million ampoule glycyrrhizin injections in 2007. Usage ratio of glass ampoules and plastic ampoules is 50% vs. 50%. Glass ampoules of glycyrrhizin injections are also widely used in Taiwan and China. Although Glycyrrhizin injections are widely used in Asian countries such as Japan, Taiwan and China, there have been no studies on particle contamination at the time of ampoule cutting. Therefore, we compared particle contamination in glycyrrhizin injection samples of various pharmaceutical companies at the time of ampoule cutting between glass and plastic ampoules. The number of particles was markedly higher for glass than for plastic ampoules (mean number of particles with a diameter of 1.3- < 5 μm was 252.9/mL for glass ampoules, 43.0/mL for plastic ampoules). Particles in glycyrrhizin samples contained in glass ampoules after ampoule cutting were identified as glass fragments by scanning electron microscopy and X-ray microanalysis. In glycyrrhizin samples in plastic ampoules after ampoule cutting, no particles were confirmed by the same analysis. Particles in plastic ampoules are assumed to be ingredient of injection oneself, or dust. We think that further identification of particles in plastic ampoules will be necessary in future. Pharmaceutical companies manufacture injections according to the criteria of the Foreign Insoluble Matter Test for Injection proposed by the Pharmacopoeia of Japan. According to the criteria, the numbers of insoluble particles with a diameter ≥ 10 μm and those with a diameter ≥ 25 μm in 1 mL of injection should be ≤ 25 and ≤ 3, respectively. Therefore, the numbers of insoluble particles with these diameters contained in injections are considered to be in these ranges during the ampoule manufacturing process.

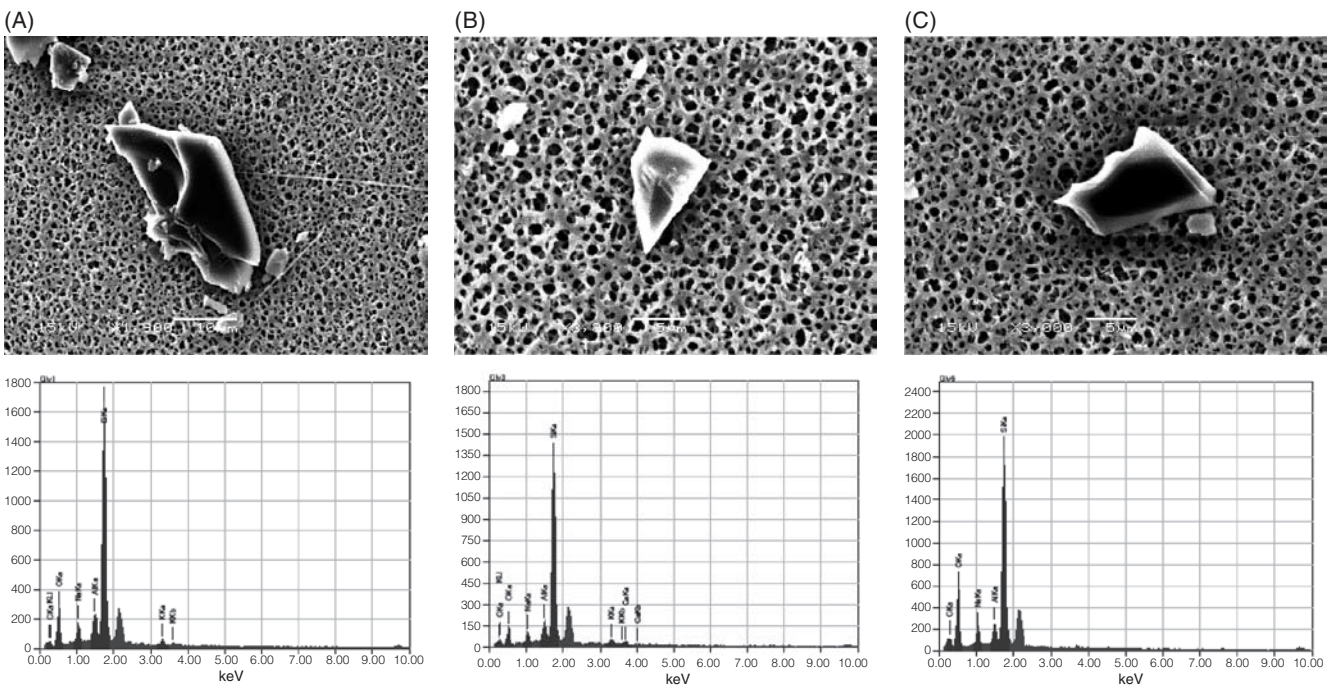

Figure 1. Identification of three types of particles by scanning electron microscopy and energy dispersion spectroscopy (A), (B) and (C) are glass fragments.

In general, since the pressure inside glass ampoule is negative due to heat sealing, glass fragments at the time of ampoule cutting are drawn into the ampoule. Indeed, this survey revealed the mixture of a large amount of glass fragments in glycyrrhizin samples after glass ampoule cutting. Most glass fragments were within a diameter of 1.3-5 μm. Since the limit of particles that can be visually observed is 40-50 μm, the detection of glass fragments with a diameter of 1.3-5 μm in injections contained in glass ampoules is difficult. Even if ampoules are cut and left for 3 minutes after ampoule cutting, glass fragments with a diameter of 1.3-5 μm may not settle but remain suspended in injections. Therefore, at the time of aspiration of injections using a syringe, there is a risk of the aspiration of glass fragments with a diameter of 1.3-5 μm suspended in injections after ampoule cutting. In fact, our previous study clearly showed that a large amount of glass fragments in total parenteral nutrition or intravenous infusion admixed with glass ampoule drugs were detected[9,10]. This result was consistent with our previous study that most of glass fragments were with a diameter of 1.3-5 μm.

It is ideal to filtrate injections after cutting glass ampoules using a membrane filter to remove particles such as glass fragments in a clean bench or safety cabinet by a pharmacist immediately before injection. However, such a procedure is not realistic in terms of labor, time and cost. Injection needles with a filter can be used, but this filter allows the removal of particles with a diameter of 10 μm or more but not those of 1.3-5 μm. This survey revealed the presence of a mixture of a large amount of glass fragments with a diameter of 1.3-5 μm that can not be macroscopically observed in injection samples after the cutting of glass ampoules. In injection samples of plastic ampoules, no particles such as glass fragments were observed after ampoule cutting, and the number of particles was much lower than that in injection samples of glass ampoules. Plastic containers include those made of polypropylene or polyvinyl chloride. To improve moldability, a plasticizer such as diethylhexyl phthalate and phthalate has been added to these containers. This plasticizer sometimes leaches from plastic containers into injections, causing particles. Therefore, plastic containers without diethylhexyl phthalate should be selected for injections. The material of plastic ampoules in Japan is mostly low-density polyethylene without diethylhexyl phthalate. Since the material of all plastic ampoules for glycyrrhizin injections investigated in this study was low-density polyethylene, particle contamination due to leaching of the components of plastic containers was unlikely. On the other hand, in glass ampoules, ion exchange between Na^+ and H^- ions in glass occurs, and Na^+ ions in glass are transferred into injections and bind to OH^- ions, forming NaOH. As a result, the injection becomes alkaline, and pH-associated incompatibility of combined drugs may reduce the main drug content or induce sedimentation, resulting in particle formation. In addition, glass ampoules involve the risk of injury at the time of ampoule cutting.

Glass fragments in injections can potentially cause fatal pulmonary thrombosis. When particles cannot be removed using filters by pharmacists, it is desirable to use injection containers with no risk of contamination or injury at the time of ampoule cutting, which may occur using glass ampoules. Therefore, for the prevention of particle contamination and safe ampoule cutting, the use of plastic rather than glass ampoules is recommended for glycyrrhizin injections that are administered at a high dose for a long period.

REFERENCES

1. DeLuca, P. P., Rapp, R. P., Bivins, B. and Griffen, W. O. 1975. Filtration and infusion phlebitis: a double-blind prospective clinical study. Am. J. Hosp. Pharm. 32: 1001-1007.
2. Schroeder, H. G. and DeLuca, P. P. 1976. Particulate matter assessment of a clinical investigation on filtration and infusion phlebitis. Am. J. Hosp. Pharm. 33: 543-546.
3. Falchuk, K. H., Peterson, L. and McNeil, B. J. 1985. Microparticulate-induced phlebitis. Its prevention by in-line filtration. N. Engl. J. Med. 312: 78-82.
4. Turco, S. J. and Davis, N. M. 1971. Detrimental effects of particulate matter on the pulmonary circulation. J. Am. Med. Assoc. 217: 81-82.
5. Lye, S. T. and Hwang, N. C. 2003. Glass particle contamination: is it here to stay? Anaesthesia 58: 84-105.
6. Walpot, H., Franke, R. P., Burchard, W. G. Agternkamp, C., Müller, F. G., Mittermayer, C. and Kalff, G. 1989. Particulate contamination of infusion solutions and drug additives within the scope of long-term intensive therapy. 1. Energy dispersion electron images in the scanning electron microscope-REM/EDX. Anaesthesia 38: 544-548.
7. Puntis, J. W. L., Wilkins, K. M., Ball, P. A., Rushton, D. I. and Booth, I. W. 1992. Hazards of parenteral treatment: do particles count? Arch. Dis. Child. 67: 1475-1477.
8. Kirkpatrick, C. J., Bittinger, F., Klein, C. L. and Hauptmann, S. 1996. The role of the microcirculation in multiple organ dysfunction syndorome (MODS): a review and perspective. Virchows Arch. 427: 461-476.
9. Oie, S. and Kamiya, A. 2005. Particulate and microbial contamination in in-use admixed parenteral nutrition solutions. Biol. Pharm. Bull. 28: 2268-2270.
10. Yorioka, K., Oie, S., Oomaki, M., Imamura, A. and Kamiya, A. 2006. Particulate and microbial contamination in in-use admixed intravenous infusions. Biol. Pharm. Bull. 29: 2321-2323.