Ceftriaxone sodium preparation for injection is known to form insoluble microparticles with calcium. The purpose of this study was to evaluate the role of an impurity in the ceftriaxone sodium preparation on this incompatibility. Firstly, using HPLC, two impurities were identified in the ceftriaxone sodium solution. The major impurity (impurity 1) was identified as tetrahydro-2-methyl-3-thioxo-1,2,4-triazine-5,6-dione by LC/MS. Second, the role played by this impurity in the incompatibility with calcium was examined. Using seven different ceftriaxone preparations for injection, the effect of adding impurity 1 to mixed solutions of ceftriaxone sodium and calcium chloride on the appearance of insoluble microparticles, was examined using a light obscuration particle counter. Although incompatibility was not completely suppressed by the addition of impurity 1, the number of insoluble microparticles formed with calcium chloride solution was decreased in proportion to the concentration of impurity 1, and the concentration of calcium ion decreased as the concentration of added impurity 1 increased. These results show that impurity 1 plays a concentration-dependent role in incompatibility between ceftriaxone sodium preparation for injection and calcium-containing solutions.

**Key words** ceftriaxone; calcium; incompatibility; impurity; insoluble microparticle; injection

Ceftriaxone (Fig. 1(a)) easily forms insoluble microparticles when mixed into even low concentrations of calcium-containing solutions. The U.S. Food and Drug Administration (FDA) have twice issued safety alerts, due to fatal adverse effects caused by ceftriaxone–calcium precipitates in lungs and kidney. In Japan, the drug package insert states under Precautions, that ceftriaxone and calcium-containing preparations should not be administered simultaneously, although up to now no safety alerts have been issued. In clinical practice, ceftriaxone is often used in combination with calcium-containing preparations providing extracellular fluid supplementation. This concomitant administration risks serious adverse effects due to the formation of insoluble microparticles which cannot be identified visually in mixed solutions such as peripheral parenteral nutrition fluid or in the Y-injection site of an intravenous line.

There have been some reports that evaluated the risk of invisible microparticles using a light obscuration particle counter. We have previously compared original and generic versions of ceftriaxone sodium preparations with regard to incompatibility with calcium-containing preparations by measuring the number of insoluble microparticles using a light obscuration particle counter. In that study, we showed that the formation of insoluble microparticles was influenced by the calcium ion concentration, storage time and shaking conditions and that the appearance of insoluble microparticles differed between preparations. We also observed impurities in the ceftriaxone sodium preparations for injection, and examined the insoluble microparticles formed in the presence of calcium solutions using HPLC. The impurity content was found to vary between preparations, with the preparations which most easily formed insoluble microparticles tending to have a lower impurity content, but experiments to investigate this phenomenon in detail were not performed.

It has been reported that some impurities can prevent crystal growth. We therefore developed the hypothesis that an impurity found to varying degrees in ceftriaxone sodium preparations for injection inhibits the formation of ceftriaxone–calcium salts. The aim of this study was therefore to examine differences in calcium incompatibility between various ceftriaxone sodium preparations for injection in relation to their impurity content. Three impurities are described in the Japanese Pharmacopoeia under purity test. As described in the examination conditions, impurity 1 is a triazine compound (Fig. 1(b)), impurity 2 is a methoxyimino geometric isomer (Fig. 1(c)), and a third impurity, a triazine adduct, was identified in the examination conditions of related substance 2 (Fig. 1(d)). Impurity 1, which is tetrahydro-2-methyl-3-thioxo-1,2,4-triazine-5,6-dione, is the major impurity and is used in the production of ceftriaxone sodium intermediate. We used impurity 1 in this study.

In this study, we quantified the formation of insoluble microparticles using a light obscuration particle counter, in order to examine differences in incompatibility between ceftriaxone and calcium solutions in varying concentrations of impurity 1. It was assumed that, under clinical conditions, the mixing of an intravenous fluid in an administration set with a secondary additive through a Y-injection site occurs in a 1:1 ratio. In case of this inline mixing, 100 mL of 2.5 mmol/L calcium-containing solution were mixed 100 mL of 10 mg/mL ceftriaxone isotonic sodium chloride solution, so that the final calcium concentration became 1.25 mmol/L and ceftriaxone concentration became 5 mg/mL. We examined the effect of impurity 1 on the calcium ion concentration and crystal morphology, in...
order to understand the mechanism of incompatibility inhibition.

**Experimental**

**Materials** The original ceftriaxone sodium preparation (A) and six generic preparations (B to G) used in the study are summarized in Table 1. Commercially available isotonic sodium chloride solution (Terumo Co., Ltd., Tokyo, Japan) and calcium chloride injection 2% (Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan) were used in this study. Tetrahydro-2-methyl-3-thioxo-1,2,4-triazine-5,6-dione (Sigma-Aldrich Inc., St. Louis, MO, U.S.A.) was used as impurity 1.

**Determination of Impurity and Confirmation of the Content of Impurity 1**

Ceftriaxone solutions was prepared by dissolving each of the seven ceftriaxone preparations for injection in the ultrapure water to a final concentration of 2 mg/mL. The determination of impurity 1 in the solutions was confirmed using LC/MS and LC-MS/MS methods. Mass measurement was conducted using a Quattro Premier (Waters Co., Milford, MA, U.S.A.). Electrospray ionization (ESI) was performed in negative ionization mode Q1 scan (mass range: from m/z 80 to 250). The mass spectra were obtained using the following optimized MS conditions, the capillary voltage, 1.0 kV; cone gas flow, 100 L/h; desolvation gas flow, 1000 L/h; source temperature, 120°C and desolvation temperature, 400°C. The collision energy was optimized for product ion (15 eV). For HPLC, 10 µL was injected onto a chromatograph (Alliance HT Waters 2795; Waters Co.) equipped with column (COSMOSIL Packed Column HILIC 2.0 mm i.d.×150 mm; Nacalai Tesque, Inc., Kyoto, Japan). The column was kept at 30°C. The mobile phase consisted of acetonitrile–10 mmol/L ammonium acetate (7:3), at a flow rate of 0.5 mL/min.

**Table 1. Preparations Used in This Study**

| Preparations | Company |
|--------------|---------|
| A ROCEPHIN® Intravenous 1 g | Chugai Pharmaceutical Co., Ltd., Tokyo, Japan |
| B Ceftriaxone sodium hydrate | Nichi-iko Pharmaceutical Co., Ltd., Toyama, Japan |
| C LIASOPHIN for intravenous injection 1 g | Chemix Inc., Kanagawa, Japan |
| D CEFXONE | Shiono Chemical Co., Ltd., Tokyo, Japan |
| E Ceftriaxone Na for intravenous (i.v.) injection 1g “TEVA” | Teva Pharma Japan Inc., Aichi, Japan |
| F CEFTRIAXONE sodium hydrate for injection 1 g [Phizer] | Pfizer Japan Inc., Tokyo, Japan |
| G CEFTRIAXONE Na | Sawai Pharmaceutical Co., Ltd., Osaka, Japan |
Determination of the Content of Impurity 1 in the Ceftriaxone Sodium Preparation for Injection

One set of ceftriaxone solutions was prepared by dissolving each of the seven ceftriaxone preparations for injection in the mobile phase to a final concentration of 2 mg/mL; these solutions were used for confirmation of impurities content. A second set of seven ceftriaxone solutions, concentration 5 mg/mL, containing 0, 20 or 40 μg/mL of impurity 1, was used for determination of impurity. The concentrations of ceftriaxone and any impurities in the solutions were confirmed using HPLC, by a method essentially the same as that described in the Japanese Pharmacopoeia, 16th ed.\(^9\) For HPLC, 10 μL was injected onto a chromatograph (LC-2010C\(_{18}\), Shimadzu Corporation, Kyoto, Japan) equipped with a detector, an integrator and reverse-phase column (CAPCELL PAK C18 UG120 S5: 4.6 mm i.d.×250 mm; Shiseido Co., Ltd., Tokyo, Japan). The column was kept at 25°C. The mobile phase consisted of acetonitrile containing tetra-n-heptylammonium bromide 4.00 g, 450 mL; water 490 mL; 40.9 mmol/L \(\text{Na}_2\text{HPO}_4\) +25.9 mmol/L \(\text{KH}_2\text{PO}_4\), 55 mL; 96.4 mmol/L citric acid monohydrate +196.3 mmol/L NaOH, 5 mL, at a flow rate of 1.5 mL/min. The wavelength was set at 254 nm.

**Inhibition of Ceftriaxone–Calcium Crystal Formation by Impurity 1**

**Measurement of Microparticles**

Appropriate volumes of 2% (w/v) calcium chloride solution (1.25 mmol/L) were added to each of the seven ceftriaxone solutions (5 mg/mL) containing varying amounts of impurity 1 (0, 20, 40 μg/mL). The solutions were mixed by inverting five times and stored at 25°C. The number of insoluble microparticles was measured using a light obscuration microprocessor (KL-04; RION Co., Ltd., Tokyo, Japan) 0, 5, 10, 30 and 100 min after mixing. The method used is essentially the same as that described in the Japanese Pharmacopoeia, 16th ed.\(^9\) For HPLC, 10 μL was injected onto a chromatograph (LC-2010C\(_{18}\); Shimadzu Corporation, Kyoto, Japan) equipped with a detector, an integrator and reverse-phase column (CAPCELL PAK C18 UG120 S5: 4.6 mm i.d.×250 mm; Shiseido Co., Ltd., Tokyo, Japan). The column was kept at 25°C. The mobile phase consisted of acetonitrile containing tetra-n-heptylammonium bromide 4.00 g, 450 mL; water 490 mL; 40.9 mmol/L \(\text{Na}_2\text{HPO}_4\) +25.9 mmol/L \(\text{KH}_2\text{PO}_4\), 55 mL; 96.4 mmol/L citric acid monohydrate +196.3 mmol/L NaOH, 5 mL, at a flow rate of 1.5 mL/min. The wavelength was set at 254 nm.

**Influence of Impurity 1 on Ceftriaxone–Calcium Crystal Morphology**

Appropriate volumes of 2% (w/v) calcium chloride solution (1.25 mmol/L) were added to each of the seven ceftriaxone solutions (5 mg/mL) containing various concentrations of added impurity 1 (0, 20, 40 μg/mL) to make a final calcium ion concentration of 1.25 mmol/L. Ceftriaxone–calcium crystal morphology was observed using a stereomicroscope (SZX10; Olympus Co., Ltd., Tokyo, Japan).

**Results**

**Determination of Impurity and Confirmation of the Content of Impurity**

Total ion current chromatograms of the ceftriaxone sodium preparations for injection are shown in Fig. 2. In all preparations, we observed peak at retention time 4.5 min. The size of the peak of impurity 1 varied between preparations; in some generic preparations, the impurity 1 ratio was higher than that of the original preparation. The mass spectrums of preparation A and impurity 1 at retention time 4.5 min are shown in Fig. 3. In all preparations, product ion spectra were similar. The relative intensity of \([\text{M}−\text{H}]^{−}\) \(m/z\) 158 was observed in all ceftriaxone sodium preparations for injection and corresponded to the deprotonated molecule of impurity 1 by the product ion spectrum of the ion \(m/z\) 158 matched that of impurity 1 sample (Fig. 4). These results indicate that this peak was confirmed as tetrahydro-2-methyl-3-thioxo-1,2,4-triazine-5,6-dione by this peak at \(m/z\) 158 cor-

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**Fig. 2.** Total Ion Current Chromatograms of the Ceftriaxone Sodium Preparations for Injection

Total ion current chromatograms of original and generic preparations of ceftriaxone sodium preparations for injection (A–G).
responded to the deprotonated impurity 1 ion.

Representative chromatograms of the different ceftriaxone sodium preparations for injection are shown in Fig. 5. In all preparations, we observed two peaks at retention times 3.9 min and 9.4 min, in addition to the main ceftriaxone peak. The peak at retention time 3.9 min, which has the larger peak area, corresponds to the retention time of tetrahydro-2-methyl-3-thioxo-1,2,4-triazine-5,6-dione, in the other words the triazine compound (impurity 1) which is a known related substance of ceftriaxone. This peak was confirmed as tetrahydro-2-methyl-3-thioxo-1,2,4-triazine-5,6-dione, as the peak area increased in proportion to the concentration of added impurity.

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**Fig. 3.** Mass Spectra of Ceftriaxone Sodium Preparation for Injection

Mass spectra of the peak at retention time of 4.5 min of (a) preparation A and (b) impurity 1. Mass spectra data indicate that [M−H] of ceftriaxone sodium preparations for injection was m/z 158.

**Fig. 4.** Product Ion Spectra of Ceftriaxone Sodium Preparation for Injection

Product ion spectra of m/z 158 of (a) preparation A and (b) impurity 1.

**Fig. 5.** HPLC Chromatograms of Ceftriaxone Sodium Preparations for Injection

Representative chromatograms of original and generic preparations of ceftriaxone sodium preparations for injection (A–G). (a) Impurity 1, (b) Ceftriaxone, (c) Peak 1.
1. The size of the peak of impurity 1 varied between preparations; in some generic preparations, the impurity 1 ratio was higher than that of the original preparation. These results support the results of LC/MS study. The content of impurity 1 in the ceftriaxone sodium preparation for injection is shown in Fig. 6. The concentration of impurity 1 ranged from 4.0 to 8.1 μg/mL. The peak at retention time 9.4 min also varied between preparations, but in all preparations, the content of this impurity was below 0.1%.

Measurement of Microparticles Temporal changes in the number of insoluble microparticles with a diameter ≥10 μm formed when 2% (w/v) calcium chloride solution (1.25 mmol/L) was added to the seven solutions of ceftriaxone sodium preparation for injection (5 mg/mL) containing varying concentrations of impurity 1 (0, 20, 40 μg/mL), are shown in Fig. 7 (note differences in scale on y axis). There were differences in the number of insoluble microparticles between preparations when without added impurity 1. The number of microparticles decreased in proportion to the concentration of impurity 1 in all preparations. In preparations B and F, which

![Fig. 6. Content of Impurity 1 in the Ceftriaxone Sodium Preparations for Injection](image)

The concentration of impurity 1 in the ceftriaxone sodium preparations for injection (mean of three observations) for each preparation. Samples were prepared by dissolving each of the seven ceftriaxone sodium preparations for injection in mobile phase to final concentrations of 2 mg/mL at 25°C.

![Fig. 8. Correlation between Calcium Ion Concentration and Impurity 1 Concentration](image)

The line indicates the correlation between the concentration of calcium ion and the concentration of impurity 1.

![Fig. 7. The Number of Insoluble Microparticles in Ceftriaxone Solutions Mixed with Known Concentrations of Impurity 1 and Calcium Chloride Solution](image)

The influence of impurity 1 on the number of insoluble microparticles with diameter ≥10 μm (mean of three observations) formed when impurity 1 (0, 20 or 40 μg/mL) and 2% (w/v) calcium chloride solution (1.25 mmol/L) were added to ceftriaxone solutions (5 mg/mL) and stored at 25°C, measured using a light obscuration particle counter. –––: Allowable microparticles.
were found to have a lower impurity 1 content, microparticles seemed to form more easily compared with the other preparations. In preparation B without added impurity 1 at 30 min after mixing and with added impurity 1 concentrations of 20 or 40 µg/mL, the number of insoluble microparticles at 60 min after mixing exceeded the permissible range for injection preparations administered at a volume of ≥100 mL in all samples (the tolerated number of insoluble microparticles with a diameter ≥10 µm is ≤25 per mL, and with a diameter ≥25 µm is ≤3 per mL). In preparation F without added impurity 1 at 30 min, the number of insoluble microparticles also exceeded the permissible range. By 60 min after sample preparation, the number of microparticles was under the permissible range in the other preparations. However, no significant correlation was found between impurity 1 content in the seven ceftriaxone sodium preparations for injection and number of insoluble microparticles.

**Influence of Impurity 1 on the Calcium Ion Ratio in Mixed Solutions** Following the addition of impurity 1 (0, 4, 8, 20 or 40 µg/mL) to 2% (w/v) calcium chloride solution (1.25 mmol/L), the calcium ion concentration in the sample solutions was found to be decreased in proportion to the concentration of impurity 1. A significant correlation was found between the calcium ion concentration and the impurity 1 concentration (Fig. 8). In concentration of impurity 1 contained ceftriaxone sodium preparations for injection (4.0–8.1 µg/mL), the decrease in calcium ion concentration was calculated to be 0.08–0.17 mmol/L. Total calcium concentration remained unchanged.

**Influence of Impurity 1 on Ceftriaxone–Calcium Crystal Morphology** Stereomicroscopic photographs of ceftriaxone–calcium crystals formed after the addition of 2% (w/v) calcium chloride solution to the seven ceftriaxone solutions (5 mg/mL) containing varying concentrations of impurity 1 (0, 4 or 40 µg/mL), are shown in Fig. 9. The number of microparticles and the particle size varied according to the amount of impurity 1 added. In sample solutions containing higher concentrations of impurity 1, fewer microparticles with a smaller particle size were observed compared with sample solutions without any impurity 1 (control).

**Discussion**
In our previous study, we demonstrated that the insoluble microparticles formed when calcium chloride injection 2% solution was added to original and generic forms of ceftriaxone sodium preparation for injection, varied significantly in appearance. Preparations in which insoluble microparticles were easily visible had a low impurity content, while those in which insoluble microparticles were barely visible had a high impurity content. We therefore concluded that the impurity content of the various ceftriaxone sodium preparations affected the formation of insoluble microparticles.

The aim of the present study was to examine the effect of the major impurity in ceftriaxone sodium preparations, impurity 1, on the appearance of insoluble microparticles in mixtures of ceftriaxone sodium and calcium-containing solutions. The other impurities were not investigated in the present study, as it is not considered that these impurities influence incompatibility. We confirmed the identity of impurity 1 as tetrahydro-2-methyl-3-thioxo-1,2,4-triazine-5,6-dione. This compound may be an ingredient used in the manufacture of ceftriaxone sodium, so it is possible that some unused material remains in the preparation. We showed that this impurity may affect the appearance of insoluble microparticles, as both the number of insoluble microparticles and their particle size were decreased in proportion to the impurity 1 concentration after the addition of calcium chloride solution. The number of insoluble microparticles was different between preparations. It is possible that differences in the appearance of the insoluble microparticles in the various preparations are due to different additives, pH, and/or impurities in the preparations themselves. There was no mention of additives on the package inserts of the products, and we previously reported no influence of pH on the appearance of insoluble microparticles. Therefore it is probable that the impurity 1 content in ceftriaxone sodium preparations for injection affects the appearance of the insoluble microparticles. However, no significant correlation was found between the contents of the impurity 1 and formation of insoluble microparticles. Multiple factors (shaking strength, impurities, crystallization rate, etc.) affect incompatibility, and it does not seem to be possible to predict the appearance of insoluble microparticles on the basis of any single factor. Therefore further examination is necessary.

Crystallization processes consist of nucleation and crystal growth. Supersaturated solutions are necessary for the initiation of nucleation. The degree of supersaturation, i.e., the difference between the solubility product and ionic product, determines the crystallization reaction. In addition, the concentration of the dissolved substances influences the process of crystal growth; the crystal growth rate can be expressed as a function of the degree of supersaturation. For example, it has been shown that many kinds of substances (metal ions, proteins, etc.) inhibit the nucleation and crystal growth of hydroxyapatite (HAP). HAP is formed by trans-
formation from calcium phosphate. Hidaka et al. reported that phosvitin, a phosphoprotein, inhibits calcium phosphate precipitation. They showed that the inhibitory effect of phosvitin on the formation of calcium phosphate precipitates was caused by a decrease in calcium concentration due to the calcium-chelating activity of phosvitin.\(^{19}\) The dion moiety which is a part of impurity 1 is known to chelate with metal.\(^{20}\) In case of impurity 1, it is suggested that dion moiety of impurity 1 was chelated with calcium ion as the calcium ion concentration is decreased in proportion to the increase in concentration of impurity 1. Onuma also suggested that phosvitin adsorbs calcium phosphate, and inhibits calcium phosphate crystal growth and transformation from calcium phosphate to HAP.\(^{21}\) Chen et al. and Koutsopoulos and Dalas reported that L-Lys inhibits the crystal growth of HAP in a concentration-dependent manner.\(^{22,23}\) L-Lys has a strong adsorption ability and easily forms an adsorption layer on the surface of HAP to inhibit crystal growth. Also, Kubota suggested that similar molecular structure of additives inhibits crystal growth.\(^{24}\) It was suggested that impurity 1 adsorbs ceftriaxone–calcium salt, and inhibits ceftriaxone–calcium salt crystal growth. These reports indicated that nucleation and crystal growth may be inhibited by substances which do not themselves influence crystallization. This supports our argument that nucleation and crystal growth involved in the formation of a ceftriaxone–calcium salt was inhibited by impurity 1.

Figure 10 represents the assumed crystallization process in ceftriaxone–calcium supersaturated solutions. In the absence of impurity 1 (Fig. 10(a)), ceftriaxone and calcium seem initially to easily form small nuclei. Gradually, the small nuclei grow to form larger crystals due to precipitation by linkage or adhesion between smaller particles. In the presence of impurity 1 (Fig. 10(b)), it is suggested that the calcium ion concentration is decreased in a concentration-dependent manner by an interaction between impurity 1 and calcium, resulting in a decrease in the degree of supersaturation and a consequent inhibition of nucleation (Fig. 10(b) middle). The inhibition of crystal growth rate may be due to adsorption of impurity 1 on the crystal surface, as it occurred in proportion to the concentration of impurity 1, and was confirmed by microscopic observation (Fig. 10(b) right).

These results suggest that differences in impurity 1 content may affect compatibility when mixing ceftriaxone sodium preparations and calcium-containing solutions. In clinical practice, ceftriaxone sodium preparations are administered over a period of 60 min. Therefore, when mixed directly with calcium-containing preparations, there is a risk of incompatibility occurring during the 60 min infusion, as the number of microparticles in preparations with a low impurity content may exceed the permissible range.

In general, pharmaceutical preparations without high levels of impurity are preferred due to the probability of fewer adverse effects, and comparisons between original and generic formulations often focus on differences in quality between...
However, in ceftriaxone sodium preparations for injection, the presence of impurities may decrease the risk of insoluble particles forming in mixtures with calcium-containing solutions. Concerns about safety due to impurity content may therefore be unfounded in this case, especially as there have not been any reported adverse effects ascribed to switching between original and generic preparations.

**Conclusion**

The major impurity (impurity 1) contained in ceftriaxone sodium preparation for injection was confirmed as tetrahydro-2-methyl-3-thioxo-1,2,4-triazine-5,6-dione. Ceftriaxone–calcium salt formation could be inhibited by the addition of impurity 1 to ceftriaxone sodium preparations. These results suggest that the presence of low levels of impurity 1 in ceftriaxone sodium preparation for injection may contribute to inhibition of incompatibility.

**Conflict of Interest**

The authors declare no conflict of interest.

**Supplementary Materials**

The online version of this article contains supplementary materials.

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