Determination of Aluminum in Large Volume Parenteral Drug Products Used in Total Parenteral Nutrition Therapy by ICP-MS with a Dynamic Reaction Cell

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The proposed method was developed for the determination of aluminum (Al) in large volume parenteral (LVP) drug products used in total parenteral nutrition (TPN) therapy. The determination of Al in LVP drug products was performed by an inductively coupled plasma mass spectrometer equipped with a dynamic reaction cell (DRC-ICP-MS). DRC-ICP-MS conditions for the analysis of Al were studied to obtain the best signal to background (S/N) ratios. The interfering polyatomic ions at mass 27 (Al) were reduced by using NH_3 as a reaction gas. The detection limit of Al in a 1% (v/v) HNO_3 aqueous solution was 2 ng/l. The Al contents in LVP drug products obtained by this method were in the range of 1.16—4.33 μg/l and were less than 25 μg/l, that is, the regulation value of Food and Drug Administration (FDA). In order to trace the origin of Al in LVP drug products, each part of the LVP drug product, which is composed of three chambers, was investigated. However, a clear difference of the Al contents in each chamber was not observed. Furthermore, the Al contents in injection bags were quantified. Although the Al contents in injection bags were relatively high (in the range of 27.5—33.6 μg/g), dissolution of Al from the injection bags was not observed in the stability testing. From all of these results, it was concluded that the Al contents in the LVP drug products investigated originated in the amount of the Al in each raw material.

Key words aluminum; large volume parenteral; total parenteral nutrition; inductively coupled plasma mass spectrometry; dynamic reaction cell

Most total parenteral nutrition (TPN) therapy is used for patients who cannot or should not get their nutrition through eating. TPN mainly consists of amino acids, carbohydrates, electrolytes, vitamins and essential trace elements. According to the condition of health, TPN may contain all or some of these substances. TPN solutions are usually made up in liter batches and used for long-term administration. Since there may be a possibility of contamination of aluminum (Al) from raw materials and injection bags used in TPN, determination of the Al contents in TPN is very important. It's noted that Al causes damage to the central nervous system and bone toxicity, especially in premature infants and patients with impaired kidney function who receive TPN therapy for long-term administration.[1—3] Therefore, the Food and Drug Administration (FDA) announced the regulations on the Al contents of large volume parenteral (LVP) drug products used in TPN therapy by 21CFR201.323.[4—7]

FDA regulates that the Al contents of LVP drug products used in TPN therapy must not exceed 25 μg/l, and the assay method to determine the Al contents must be validated. In response to the regulations, the analytical method for Al in LVP drug products was investigated at the Pharmaceutical Manufacturers' Association of Tokyo, the Osaka Pharmaceutical Manufacturers Association and each pharmaceutical company in Japan.[8] However, the general test for Al in LVP drug products that can be shared between companies has not still been included in the Japanese Pharmacopoeia Fifteenth Edition (JP XV).[9] Only analytical methods of high performance liquid chromatography-fluorescence detection (HPLC-FL), using two kinds of fluorescent chelating agents, quinolinol[10,11] and lumogallion,[12] are described in general information of JP XV. Therefore, each company develops the analytical method in their way, and controls their products.

To determine the Al contents in LVP drug products, highly sensitive analytical methods such as HPLC-FL,[10—13] atomic absorption spectrometry (AAS),[14] inductively coupled plasma atomic emission spectrometry (ICP-AES)[15] and inductively coupled plasma mass spectrometry (ICP-MS)[16] are required. In addition, the use of these methods may be limited due to the matrix such as amino acids, carbohydrates and electrolytes. Thus, the selection of a suitable analytical method is needed.

ICP-MS is one of the most sensitive methods, and furthermore, dynamic reaction cell (DRC) technique that enables us to reduce the interfering polyatomic ions on the analyte of interest. DRC is known as an effective method for alleviation of interferences. In this study, DRC technique enables us to reduce the interferences at m/z 27 caused by $^{9}Be^{18}O^{+}$, $^{10}B^{17}O^{+}$, $^{11}B^{16}O^{+}$, $^{12}C^{15}N^{+}$ and $^{13}C^{14}N^{+}$ on $^{27}Al^{+}$. Especially in LVP drug products, the interfering polyatomic ions such as $^{12}C^{15}N^{+}$ and $^{13}C^{14}N^{+}$ are remarkable. Therefore, the proposed method was developed with ICP-MS equipped with a dynamic reaction cell (DRC-ICP-MS). DRC-ICP-MS is composed of four major components, an ICP source, an ion lens, a DRC and a quadrupole mass spectrometer. DRC is located in the vacuum chamber between the cylinder lens and the quadrupole mass spectrometer. A cylinder lens focuses sample ions coming from the skimmer cone. The focused ions are directed into DRC. DRC can be pressurized with a cell gas and DRC provides online chemical modification to eliminate interferences. Various gases, including NH_3, O_2, CH_4 and H_2, can be used as the cell gas.

The optimization of the DRC-ICP-MS technique and the results of the Al contents in LVP drug products obtained by the optimized method are described. In order to trace the origin of Al in LVP drug products, each part of LVP drug products was investigated. Moreover, dissolution of Al from the injection bags was investigated. To the best of our knowl-

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edge, this is the first report concerning the origin of the Al in LVP drug products. The results of the Al contents in LVP drug products obtained by the other methods such as ICP-AES and HPLC-FL are also described for the comparison.

Experimental

Reagents Purified water (18.2 MΩ cm) from a Milli-Q water purification system (Millipore, Tokyo, Japan) associated to an Elix3 pre-system (Millipore, Tokyo, Japan) was used to prepare all solutions. Al standard solution (1000 mg/l) was purchased from Merck (Tokyo, Japan). Standard solution for the optimization for the DRC-ICP-MS instrument was purchased from PerkinElmer (Concord, Ontario, Canada). River water reference materials for trace elements purchased from The Japan Society for Analytical Chemistry (Tokyo, Japan) were used for the evaluation of three analytical methods. Nitric acid (HNO_3) of ultrapure analytical reagents grade was purchased from Tama Chemicals (Kanagawa, Japan). 2-Propanol of trace analysis grade was purchased from Kanto Chemical (Tokyo, Japan). Argon (Ar) gas (99.999% purity) and Oxygen (O_2) gas (99.999% purity) were purchased from Taiyo Nippon Sanso (Tokyo, Japan). NH_3 gas (99.999% purity) was purchased from Sumitomo Seika Chemicals (Osaka, Japan). Al labeling kit and Neo R3 Eluent purchased from Shino-Test (Tokyo, Japan) were used for HPLC-FL.

Samples Eight different kinds of LVP drug products clinically used in TPN therapy in Japan were obtained from Mitsubishi Tanabe Seiyaku (Osaka, Japan). These are classified into three types. The first type contains amino acids, carbohydrates, electrolytes and vitamins. The second type contains amino acids, carbohydrates and electrolytes. The third type contains only amino acids. LVP drug products I, II and III are composed of three chambers, named chamber A, chamber B and chamber C to assure the stability of each active ingredient. The difference of three type LVP drug products I, II and III is the volume in chamber A and Glucose content in chamber B. Chamber A consists of nineteen amino acids and three vitamins. Chamber B consists of one carbohydrate, eight electrolytes and three water-soluble vitamins. Chamber C consists of three water-soluble vitamins and four fat-soluble vitamins.[17] Before administration, the components of the three chambers are joined together by breaking the stopper of chamber C and the barrier between chamber A and chamber B, and then mixed well without opening the bag. On the other hand, LVP drug products IV—VIII are packed in one bag. Components of the second and the third type LVP drug products are all included in the first type LVP drug products.

Instrumentations An ELAN DRC II ICP-MS instrument (PerkinElmer, Concord, Ontario, Canada) equipped with DRC was used in this study. A platinum cone, a quartz injector (2.0 mm orifice), a PC3 spray chamber and a PFA nebulizer were supplied with the instrument. The sample solutions were pumped to the spray chamber by a peristaltic pump. An AS-93 plus autosampler enclosed with a polypropylene (PP) autosampler holder was used for continuous analysis.

A multiwave 3000 microwave system (Anton Paar, Graz, Austria) equipped with polytetrafluoroethylene (PTFE) vessels was used to digest the injection bag samples.

The HPLC system consisted of a LC-10AD pump, an RF-10A_{XL} fluorescence detector, an SIL-10A autosampler, a C-R7A plus integrator and an SCL-10A system controller (Shimadzu, Kyoto, Japan). Separation was achieved with a Develosil Shinal-Neo (4.6 mm i.d.×60 mm, Nomura Chemical, Aichi, Japan) and a mobile phase of Neo R3 Eluent at a flow rate of 1.0 ml/min. Column temperature was maintained at room temperature. Fifty microliters each of the sample solution and the standard solution was injected. The Al chelate was detected at 370 nm (excitation wavelength), and 504 nm (emission wavelength). Al determination was performed according to the procedures by Shino-Test.

The ICP-AES system used was ICPS-7500 (Shimadzu, Kyoto, Japan). RF power was set at 1600 W. Coolant gas (Ar) flow rate, nebulizer gas (Ar) flow rate and purges gas (Ar) flow rate were set at 16 l/min, 0.7 l/min and 1.4 l/min, respectively. Observation height was set at low for radial mode. The Al signals were observed at 167.079 nm.

Optimization for the DRC-ICP-MS Instrument The DRC-ICP-MS instrument was run for at least 30 min with plasma before daily optimization. This procedure targets the optimization of the sample introduction system. A standard solution containing 1 μg/l of Be, Co, In, U, Mg, Rh, Pb, Na, Fe, Ca, K, Ba and Ce in a 0.5% (v/v) HNO_3 aqueous solution was used for the optimization under Standard Mode with the cell gas (NH_3) vented.

Semi-quantitative Method by DRC-ICP-MS Instrument The semi-quantitative method enables us to automatically determine the concentrations of up to 81 elements in a sample solution. This method affords an approach to characterize unknown solutions. In this study, the Al contents in sample solutions were quantified by the semi-quantitative method before the quantitative analysis. Semi-quantitative analysis was performed with the same standard solution used in 'Optimization for the DRC-ICP-MS Instrument'. Next, the Al concentrations of the standard addition solutions were decided from the results of the semi-quantitative analysis.

Sample Preparation. Sample Preparation for LVP Drug Products Al contents in LVP drug products were quantified by employing the standard addition method. Five milliliters of the LVP drug product was added to a 50 ml conical tube. Then the tube was made up to the mark with a 1% (v/v) HNO_3 aqueous solution and treated as the sample solution. A 1% (v/v) HNO_3 aqueous solution was treated as the blank solution. Five milliliters of the LVP drug product was added to each of three 50 ml conical tubes. Next a series of increasing volumes of Al standard solution diluted with a 1% (v/v) HNO_3 aqueous solution were added. The concentration and the volume of the Al standard solution were appropriately selected on the result of the semi-quantitative analysis. The Al volumes added to the conical tubes were equal, double and quadruple the Al contents in the LVP drug product quantified with the semi-quantitative method. Finally, each conical tube was made up to the mark with a 1% (v/v) HNO_3 aqueous solution and mixed well. These solutions were treated as the standard addition solutions A, B and C, respectively.

Sample Preparation for Injection Bag Injection bags made of PP were digested according to the procedure shown in Fig. 1. The Al contents in injection bags of LVP drug products were quantified by employing the standard addition method. Two-tenths gram of cut sample was weighed into a PTFE tube and 6 ml of HNO_3 was added. The sample was heated and digested by the microwave preparation system. The microwave power was set at 500 W for 10 min, and then was increased to 1000 W over 10 min and was maintained for 25 min. A Multiwave 3000 microwave system equipped with PTFE vessels was used to digest the injection bag samples. PTFE vessels equipped with PTFE lip-type seals were put into the ceramic vessel jacket and were placed together into the protective casing. They were then put into the microwave chamber. The maximum pressure and temperature in the PTFE vessels was programmed to not exceed 60 bar and 240 °C, respectively. After cooling, the digests were diluted to 20 ml with purified water, and used as the digested sample solution. Fifty microliters of the digested sample solution was added to a 50 ml conical tube. The tube was then made up to the mark with a 1% (v/v) HNO_3 aqueous solution and treated as the sample solution. A 1% (v/v) HNO_3 aqueous solution was treated as the blank solution. Fifty microliters of the digested sample solution was added to each of three 50 ml conical tubes. Then a series of increasing volumes of Al standard solution diluted with a 1% (v/v) HNO_3 aqueous solution were added. The concentration and the volume of the Al standard solution were appropriately selected on the result of the semi-quantitative analysis. The Al volumes added to the conical tubes were equal, double and quadruple the Al contents in the sample solution quantified with the semi-quantitative method. Finally, each conical tube was made up to the mark with a 1% (v/v) HNO_3 aqueous solution and mixed well. These solutions were treated as the standard addition solutions A, B and C, respectively.

Laboratory Environment The samples were prepared in the clean bench condition, controlled at class 1 (JIS B9920),[18] and the autosampler enclosed with PP autosampler holder was controlled at class 1 (JIS B9920). The laminar flow with 0.5 μm filtered air was maintained in the clean bench and the autosampler at all times. Moreover, careful attention to the contamination with Al was paid for water, solvents, reagents, vessels and other tools used during experiments for this study.

Results and Discussion

Optimization of the ICP-MS Conditions RF power, nebulizer gas (Ar) flow and cell gas (NH_3) flow were optimized to give the larger ion intensity of Al and lower background equivalent concentration (BEC) value in the sample solutions. Moreover, in order to prevent buildup of carbon on the interface cones and maintain stable ion intensity of Al, sample introduction gas (O_2) was added to the nebulizer gas flow in the cyclonic spray chamber. BEC is the concentration for the background intensity based on the sensitivity of an element. BEC value is used as an important criterion for instrument performance.

The conditions of DRC-ICP-MS were fixed as shown in Table 1. Other parameters were set at the conventional values according to the instrumental brochure.

Determination of Al in the Certified Reference Materials River water reference materials, JSAC 0301-1 (certified values 19.0±0.9 μg/l) and JSAC 0302 (certified values 67±1 μg/l) were analyzed by DRC-ICP-MS, ICP-AES and HPLC-FL. The results are summarized in Table 2. Al values determined by the three analytical methods were consistent with the certified Al value within the standard deviation except JSAC 0301-1 by HPLC-FL, showing the reliability of these three methods for the river water. Among three, good agreement (accuracy) was observed for DRC-ICP-MS. Further DRC-ICP-MS showed good precision compared with the other two methods.

Al Contents in LVP Drug Products. Al Contents in LVP Drug Products LVP drug products were diluted to 1 : 10 with a 1% (v/v) HNO_3 aqueous solution and treated as the sample solutions. A 1% (v/v) HNO_3 aqueous solution was treated as the blank solution. Al contents in LVP drug products were quantified by employing the standard addition method. DRC-ICP-MS conditions used are shown in Table 1. The results of the Al contents in LVP drug products I—VIII are summarized in Table 3. Measurements were repeated three times. For each sample, good linear relationships were found between the ion intensity and the concentration of the standard addition solutions. Al contents in LVP drug products obtained by DRC-ICP-MS were in the range of 1.16—4.33 μg/l and were less than 25 μg/l. Based on the type and the content of the raw materials used in the LVP drug products, Al contents in LVP drug products were different. Among eight LVP drug products, LVP drug products I, II and III gave higher Al contents compared with other LVP drug products. It can be ascribed to the wide variety and the content of raw materials used in these products.

To compare or confirm the Al contents, two different analytical methods, ICP-AES and HPLC-FL were employed for LVP drug products I, II and III. The comparison results are summarized in Table 4. Al contents quantified by ICP-AES were all under the detection limit (12.5 μg/l, data not shown). On the other hand, Al contents quantified by HPLC-FL were slightly higher than those by DRC-ICP-MS. The reason for the difference in the results is due to the sensitivity and accuracy in each analytical method, although high values in HPLC-FL compared with DRC-ICP-MS are still unclear.

Al Contents in Each Chamber of LVP Drug Products In order to trace the origin of Al in LVP drug products, the Al contents in each chamber of LVP drug product II were quantified by DRC-ICP-MS. LVP drug product I, II and III are composed of three chambers, named chamber A, chamber B and chamber C. Table 5 shows the results of the Al contents in each chamber of LVP drug product II by DRC-ICP-MS. Measurements of chamber A and chamber B were repeated three times. A clear difference of the Al contents in each chamber was not observed. Meanwhile, the Al contents in LVP drug product II obtained in this study ('Al Contents in LVP Drug Products') were approximately equivalent to the sum of the Al in each chamber.

Table 1. DRC-ICP-MS Conditions for Quantitative Method

Parameter	Value
RF power	1500 W
Plasma gas (Ar) flow rate	17 l/min
Auxiliary gas (Ar) flow rate	1.2 l/min
Nebulizer gas (Ar) flow rate	0.92 l/min
Ion lens	Auto lens (V)
Dwell time	500 ms/amu
Sweeps/reading	20
Readings/replicate	1
Replicates	5
Scan mode	Peak hopping
Sample uptake rate	1.0 ml/min
Sample introduction gas (O_2) flow rate	30 ml/min
Mass/analyte	^{27}Al
Cell gas (NH_3) flow rate	0.50 ml/min
RPa	0
RPq	0.6

Table 2. Determination of Al in the Certified Reference Materials

River water reference materials for trace elements	DRC-ICP-MS	ICP-AES	HPLC-FL
JSAC 0301-1 (Certified values: 19.0±0.9 μg/l)	19.4±0.2[a)]	17.9±3.7[a)]	21.2±0.5[a)]
JSAC 0302 (Certified values: 67±1 μg/l)	67.2±0.3[a)]	67.3±1.3[a)]	65.9±0.4[a)]

a) Results were means of three measurements±standard deviation.

Table 3. The Al Contents in LVP Drug Products

Large volume parenteral (component)	Al content (μg/l)[a)]
LVP drug product I (Amino acids, carbohydrate, electrolytes, vitamins)	4.33±0.20
LVP drug product II (Amino acids, carbohydrate, electrolytes, vitamins)	4.33±0.12
LVP drug product III (Amino acids, carbohydrate, electrolytes, vitamins)	4.02±0.07
LVP drug product IV (Amino acids, carbohydrate, electrolytes)	3.44±0.10
LVP drug product V (Amino acids, carbohydrate, electrolytes)	3.56±0.21
LVP drug product VI (Amino acids, carbohydrate, electrolytes)	1.16±0.07
LVP drug product VII (Amino acids)	2.05±0.12
LVP drug product VIII (Amino acids)	2.71±0.10

a) Results were means of three measurements±standard deviation.

Table 4. Comparison of the Results of the Al Contents in LVP Drug Products by DRC-ICP-MS, ICP-AES and HPLC-FL

Large volume parenteral (Component)	Al content (μg/l)		
	DRC-ICP-MS	ICP-AES	HPLC-FL
LVP drug product I (Amino acids, carbohydrate, electrolytes, vitamins)	4.33±0.20[a)]	n.d.[b)]	6.60±0.23[a)]
LVP drug product II (Amino acids, carbohydrate, electrolytes, vitamins)	4.33±0.12[a)]	n.d.[b)]	6.52±0.24[a)]
LVP drug product III (Amino acids, carbohydrate, electrolytes, vitamins)	4.02±0.07[a)]	n.d.[b)]	6.73±0.27[a)]

a) Results were means of three measurements±standard deviation. *b*) Not detectable (<12.5 μg/l).

Table 5. The Al Contents in Each Chamber of LVP Drug Product II

Chamber	Al content (μg/l)
A (300 ml)	2.63±0.06[a)]
B (700 ml)	4.55±0.02[a)]
C (3 ml)	2.01

a) Results were means of three measurements±standard deviation.

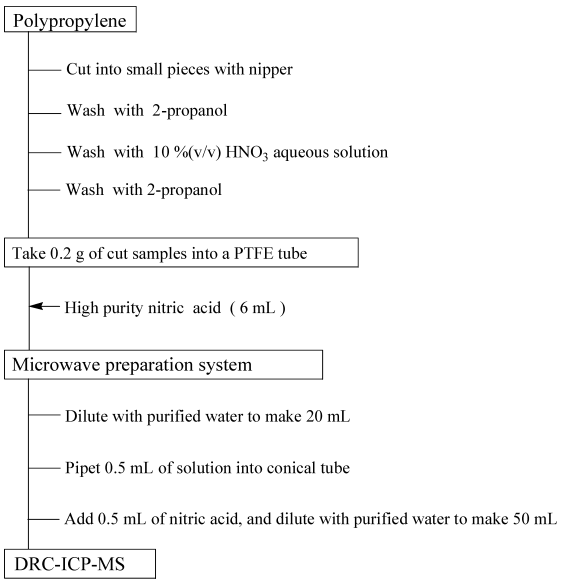

Fig. 1. Decomposition Method for Injection Bag (Polypropylene) of LVP Drug Products

Injection bags made of PP were digested according to this procedure.

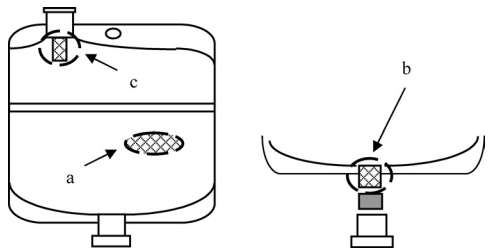

Fig. 2. Sampling Parts of the Injection Bags for LVP Drug Product II

Sampling parts of the injection bags for LVP drug product II were shown in this figure.

Dissolution of Al from Injection Bag Since there is a possibility of dissolution of Al from injection bags, the Al contents in injection bags were quantified by DRC-ICP-MS, and stability testing of LVP drug products was investigated. Injection bags made of PP were decomposed according to the procedure described in Fig. 1. Sampling parts of the injection bags for LVP drug product II are shown in Fig. 2. Sample solutions prepared from three different parts, a, b and c, were quantified by employing the standard addition method. LVP drug products are constantly exposed to these parts. Measurements were repeated three times. Table 6 shows the results of the Al contents in injection bags. As shown in Table 6, the Al contents in injection bags were in the range of 27.5—33.6 μg/g, showing a higher level of Al contents in comparison with injection liquid.

Stability of LVP drug product II was investigated under the condition of 25 °C/60% RH and 60 °C. Storage term was 24 months for 25 °C/60% RH and 4 week for 60 °C. The Al contents in these samples were quantified by employing the standard addition method. Samples were diluted to 1 : 10 with 1% (v/v) HNO_3 aqueous solution and treated as sample solution, and the results are summarized in Table 7. Although 27.5—33.6 μg/g of Al were detected in injection bags, dissolution of Al from the injection bags was not observed in the storage.

Table 6. The Al Contents in Injection Bag for LVP Drug Product II

Polypropylene	Al content (μg/g)[a)]
a	33.6±0.2
b	27.5±0.9
c	29.7±0.3

a) Results were means of three measurements±standard deviation.

Table 7. Stability Testing of LVP Drug Product II

Storage conditions, interval	Al content (μg/g)[a)]
Initial	4.20±0.18
60 °C, 4 week	4.28±0.05
25 °C/60% RH, 24 months	4.17±0.18

a) Results were means of six measurements±standard deviation.

Conclusions

DRC-ICP-MS was found to be useful for the determination of Al contents in LVP drug products. The interfering polyatomic ions on Al were reduced by using a reaction gas (NH_3). The sample introduction gas (O_2) system prevents buildup of carbon on the interface cones, leading to the stable ion intensity. The use of this method provides a simple and accurate technique to determine Al in a complex matrix such as LVP drug products without the need for a complicated sample preparation. Detection limit of Al in LVP drug products was superior to ICP-AES and HPLC-FL.[8)] The Al contents in LVP drug products I—VIII used in TPN therapy in Japan were all less than 25 μg/l, which is the regulation value of FDA. In order to trace the origin of Al in LVP drug products, LVP drug products were investigated to identify which raw material was the origin of the Al. However, the raw material that was the origin of Al was not identified. Moreover, dissolution of Al from the injection bags was not observed in the stability testing. For all of these results, the Al contents in LVP drug products obtained in this study were originated in the sum of the Al in each raw material. Therefore, it is necessary to control the Al contents in each raw material under the appropriate level.

Acknowledgements The authors thank PerkinElmer for sharing their knowledge and discussing the origin of Al.

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