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Evaluation of parenteral diluent contamination by caprolactam

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Purpose: A leachable cyclic amide (caprolactam) can be found in normal saline (NS) and 5% dextrose in water (D5W) plastic bags widely used in clinical practice if they contain polyamide in a multilayer sheeting. This contamination and the parameters that could influence its content have never been studied in a public work such as a scientific publication.

Methods: Two independent laboratories validated a caprolactam dosing method and studied contamination levels in several containers.

Results: Caprolactam content in multilayer polypropylene/polyamide/polypropylene plastic bags ranged from a mean (SD) of 5.43 (0.21) mg/L (D5W 1,000 mL) to 22.83 (1.26) mg/L (NS 50 mL). NS and D5W can be intravenously administered with a total daily dose of 3 L, corresponding to a minimal daily dose of 16.3 mg of caprolactam.

Conclusion: The high levels of contamination we have reported and the possibility of administering caprolactam to high-risk patients (eg, neonates, the elderly) should make it imperative for pharmaceutical companies to communicate publicly on the safety of caprolactam.

Keywords: caprolactam, dextrose, HPLC-UV, leachable, normal saline, polyamide

Normal saline (NS) and 5% dextrose in water (D5W) are widely prescribed and administered to hospitalized patients as fluid replacement solutions. They can be stored in various containers made from different materials. Among these, polymers are the most commonly used as they offer many advantages.¹ However, the assessment of extractables and leachables from these polymers has become an important issue in recent decades. The safety and quality of polymeric containers must be strictly controlled prior to marketing authorization, in accordance with several guidelines.²

Extractables are organic and inorganic substances released under experimental conditions, while leachables are released under normal conditions of storage and use. Leachables assessment and subsequent toxicological studies must be done by the pharmaceutical industry, but these data are often unavailable to consumers. In this context, our laboratory randomly discovered organic contamination in NS containers (Viaflo, Baxter) and decided to investigate. The suspected contaminant turned out to be caprolactam.

In the literature, caprolactam has been described as a GABA-antagonist,^{3,4} and although several toxicological studies have been carried out on animals for the oral and respiratory routes, parenteral toxicity assessments are lacking. However, caprolactam is considered to have a low toxicity to humans due to its rapid elimination.⁵

Ten years ago, Jenke⁶ described a safety risk assessment of organic extractables for parenteral drug products. He classified over 500 extractables into 4 risk score categories (low, moderate, intermediate, and high risk) to indicate whether the extractable could adversely affect patient safety as a leachable. With regard to its safety, availability, and solubility, caprolactam was classified in the intermediate risk category, with a total risk score of 31.

We present and discuss herein the results of an investigation of caprolactam contamination in various containers. These analyses were conducted in 2 independent laboratories. Moreover, a study on caprolactam variation under different conditions (time, temperature, and pH) was also performed.

Materials and methods

Chromatographic conditions. Caprolactam was quantified by high-performance liquid chromatography with ultraviolet absorption detection (HPLC-UV) in 2 independent laboratories (L1 and L2).

In L1, the chromatographic method was performed on an automatic HPLC-UV-DAD system with an XTerra RP18 3.5 μm , 4.6 \times 100 mm column (Waters). The mobile phase consisted of an aqueous solution of 20 mM sodium dihydrogenophosphate buffered to pH 2.2 with phosphoric acid. It was filtered through a Millipore 0.45 μm cellulose filter and used in isocratic mode at a flow of 0.8 mL/min for 10 minutes. The wavelength for caprolactam detection was 210 nm, injection volumes were 20 μL , and the column temperature was 25 $^{\circ}\text{C}$. Linearity was determined with 7 concentrations ranging from 1.25 to 100 mg/L prepared in sextuplicate from a caprolactam standard (caprolactam certified reference material, CRM01483-100MG, Sigma-Aldrich) dissolved in ultrapure water. Repeatability was determined from within-day variation measurements, while intermediate precision and accuracy were determined from between-day variation measurements.

In L2, the chromatographic method used an automatic HPLC-UV-DAD system (the ELITE LaChrom VWR/Hitachi plus autosampler, a VWR L-2455 photodiode array detector, and a VWR L-2130 HPLC pump). The column was a LiChrospher 5 μm , 4 \times 125 mm column (Merck). The mobile phase was a mixture of methanol and ultrapure water (70:30). It was

filtered through a Millipore 0.45 μm cellulose filter and used in isocratic mode, with a flow of 1 mL/min for 10 minutes. The wavelength for caprolactam detection was 210 nm, injection volumes were 50 μL , and the column temperature was 25 $^{\circ}\text{C}$. Linearity was determined with 5 concentrations ranging from 2 to 30 mg/L prepared in triplicate from a caprolactam standard (caprolactam, BVBV2816, Sigma-Aldrich) dissolved in ultrapure water. The intraday repeatability was evaluated as recommended by the International Conference on Harmonization (ICH) guideline Q2 (R1) using 3 determinations for each concentration (2, 10, and 30 mg/L). For interday precision, 3 determinations each for the same concentrations were assayed daily on 3 different days.

Study design. First, various NS containers (Viaflo, Baxter, 100 mL, 250, and 500 mL; Freeflex, Fresenius Kabi, 250 and 500 mL; Kabipac, Fresenius Kabi, 500 mL; Physiodose, Gilbert, 5 mL; Proamp Aguettant, 20 mL; CDM Lavoisier, 250 mL) were analyzed by direct injection. Caprolactam was quantified by HPLC-UV at laboratory L1.

Then, caprolactam quantification was conducted in 2 independent hospital laboratories (L1 and L2) to reinforce the level of evidence of the reported contamination. Each laboratory analyzed in triplicate the contents of plastic bags (23 NS- and 26 D5W-containing Viaflo plastic bags of different volumes) available in its hospital, then sent the samples (at ambient temperature, protected from light) to the other laboratory for analysis in triplicate.

Next, we decided to store these containers at different temperatures to study caprolactam variations over time. A batch of NS 100 mL (22H27G61) was selected and stored under 3 different conditions: 3 plastic bags at a temperature of 2-8 $^{\circ}\text{C}$ in a refrigerator, 3 plastic bags at 25 $^{\circ}\text{C}$ and 60% relative humidity (RH), and 3 plastic bags at 40 $^{\circ}\text{C}$ and 75% RH in 2 climatic chambers (Memmert). In the same batch, NS was also removed

from plastic bags and replaced by NS from glass containers that were previously reported as being free from caprolactam. Three plastic bags were stored at a temperature of 2-8 °C, 3 plastic bags at 25 °C and 60% RH, and 3 plastic bags at 40 °C and 75% RH. Glass containers were also stored in each condition as negative controls (free from caprolactam).

Caprolactam contamination was analyzed monthly from time 0 to 6 months.

Finally, as caprolactam is a cyclic amide, its physicochemical interactions were investigated. There are several causes of physicochemical interactions, such as pH effects and drug-drug interactions.⁷

Caprolactam content was studied at different pH levels. Acid (hydrochloric acid 0.5 or 1M) or base (sodium hydroxide 1M, 0.1M, or 0.05M) were added to 100-mL NS plastic bags to reach the target pH (2, 4, 6, 8, or 10). Plastic bags were stored for 15 days at 25 °C and 60% RH, and caprolactam content was determined at day 0 and day 15.

We also studied caprolactam content in 50-mL NS plastic bags (batch 23D19G63, Viaflo, Baxter) 3 hours after addition of commercial cisplatin (1 mg/mL; Accord). Samples were stored at ambient temperature and protected from light. Low and high cisplatin final concentrations (0.107 mg/mL and 0.5 mg/mL) were both tested.

Statistical analysis. To descriptively compare the results of caprolactam concentration measurements obtained in laboratories L1 and L2, the interlaboratory bias was calculated. The intralaboratory variance (S_L^2) was then calculated for each triplicate measured. By convention, negative S_L^2 values were set to 0. Then, the interlaboratory reproducibility of the standard deviation (S_R) was calculated for each triplicate. In order to assess the relevance of the interlaboratory comparison, the normalized deviation (E_N) was calculated for each triplicate. With an absolute E_N value of ≤ 1 , the comparison of values between the 2 laboratories is considered reliable. Finally, a comparison of the mean

caprolactam concentrations for each bag type (independent of batch) obtained by L1 and L2 was made using a Mann-Whitney test. *P* values below 0.05 were considered as statistically significant.

The relationship between variation of caprolactam content in plastic bags and time was estimated by regression analysis and calculation of the coefficient of determination (R^2). Correlation coefficient tests at a 95% confidence level were conducted between the 2 variables caprolactam concentration and time. *P* values below 0.05 were considered statistically significant.

Results

Method validations. In L1, the linearity evaluation revealed a deviation at the lowest concentration (1.25 mg/L). Thus, linearity was established between 2.50 and 100 mg/L. Repeatability, intermediate precision, and accuracy results and an example of a caprolactam chromatogram are reported in eTable 1 and eFigure 1.

In L2, linearity was established between 2 and 30 mg/L, with an R^2 of 0.999. The results of the calibration study highlight the homogeneity of the variance (Cochran's test: $C_{exp} = 0.643 < C_{th}(5\%; 3; 5) = 0.684$). Analysis of variance (nonlinearity) demonstrated the good fit of a linear model for our method ($F_{exp} = 0.10 < F_{th}(5\%; 3; 10) = 3.71$). All intraday precision values and interday precision values were less than 1.6% and 3.35%, respectively. An example of a caprolactam chromatogram is shown in eFigure 2.

Caprolactam contamination in various containers. During an HPLC method validation in the year preceding this study, we identified an extraneous peak in several NS flexible plastic containers. These containers were composed by a multilayer sheeting (polyethylene/polyamide/polypropylene). To identify the origin of this contamination,

bibliographic research was conducted. A study⁸ and a communication⁹ reported the presence of the polyamide (nylon) monomer caprolactam in the same containers.

With regard to these data, and as the extraneous peak we found and a caprolactam standard solution we analyzed under the same analytical conditions had the same retention times, we decided to investigate caprolactam contamination in several containers. The results are summarized in eTable 2.

Of the tested containers, only those made of polyamide were contaminated with caprolactam. The levels of contamination observed prompted us to pursue our investigations.

Caprolactam contamination levels in different volumes. Caprolactam contamination in NS and D5W plastic bags was compared with analyses performed by two different laboratories, L1 and L2. Results are presented in Tables 1 and 2.

The extremely low intralaboratory variance and interlaboratory reproducibility standard deviation values confirm the homogeneity of the results obtained by L1 and L2. Each normal deviation value is less than 1, demonstrating the consistency of results between L1 and L2. Interestingly, no statistical difference could be detected when comparing the mean caprolactam concentrations measured by L1 and L2 for each bag type, either NS or D5W, except for 1,000-mL NS bags ($P < 0.001$), partly due to the extremely low overall %SD recorded in both L1 and L2 for this series.

Of the 49 samples analyzed, only one had results from L1 and L2 differing by more than 5%. Caprolactam dosing methods of the two laboratories were sufficiently reliable (no E_N value of >1) to accurately estimate mean caprolactam content in containers. According to the summary of product characteristics of NS and D5W, a maximum daily volume of 3 L can be intravenously administered to patients. The total daily doses of caprolactam that could

theoretically be administered to patients in accordance with this recommendation are reported in Table 3.

Caprolactam concentrations varied with container volume. Lower volumes were associated with higher caprolactam concentrations, probably because the internal surfaces in contact with NS or D5W increase when volumes decrease (as reported in eTable 3). However, we did not identify any differences in caprolactam content between NS and D5W containers.

Change in caprolactam contamination over time. The variations in caprolactam content over time were studied. Results are summarized in eFigures 3 and 4.

Caprolactam concentrations in untouched bags showed no statistically significant relationship with storage time, whatever the storage conditions. In bags containing caprolactam-free NS from glass containers, a statistically significant relationship between time and measured caprolactam concentration was observed only for storage at 40 °C at 75% RH ($P < 0.006$).

Caprolactam physicochemical interactions. The mean (SD) pH of NS in 5 different plastic bags (Viaflo100 mL, Baxter,) was found to be 5.76 (0.05). When NS is used as a diluent, the solubilized drug may cause the pH to vary. Consequently, caprolactam content was studied at different pH levels at day 0 and at day 15. The results summarized in Table 4 show that no relevant differences were found. It seems that pH has little or no influence on the caprolactam content in NS plastic bags.

Caprolactam is a cyclic amide that can theoretically react with alkylating agents.¹⁰⁻¹² For example, caprolactam N-alkylation to produce N-methylcaprolactam was described, with dimethylsulfate used as a reagent.¹³ Dimethylsulfate is an alkylating reagent that can also react with DNA through a bimolecular substitution (S_N2) reaction.¹⁴ We hypothesized

that anticancer agents that can interact with nitrogen atoms, when diluted in NS or D5W plastic bags contaminated with caprolactam, would be at least partially inactivated and caprolactam would be N-substituted.

Cisplatin is an anticancer agent that can form covalent DNA adducts. Its interaction with N7 nitrogen of purine base was described from years as one of its main mechanism of action.¹⁵ However, addition of cisplatin (0.107 mg/mL and 0.5 mg/mL) in 50-mL NS plastic bags showed no meaningful influence on caprolactam content after 3 hours.

Discussion

In this work, we report caprolactam contamination of both NS and D5W. Caprolactam is a polyamide (nylon) monomer already described as an extractable of nylon material¹⁶ and also as a leachable of other multilayer containers.¹⁷

With regard to the summary of product characteristics, an adult patient can be infused with a maximal volume of 3 L. If 1-L NS and D5W containers are used, an adult patient can receive, respectively, approximately 16.5 mg and 16.3 mg of caprolactam per day. Moreover, the lower the volumes of container used are to reach this maximal volume of 3 L, the higher the daily quantities of caprolactam administered. It can be assumed that a patient will not be infused with 60 plastic bags of 50 mL per day (corresponding to 3 L and a theoretical caprolactam administration of 68.5 mg with use of NS and 66.7 mg with use of D5W), but small volumes are often used as diluents for various intravenous medications.

Pediatric patients can also be infused using such containers, which can also be used to provide parenteral nutrition to high-risk patients such as neonates. Patients with renal or hepatic insufficiencies and pregnant women can also be infused, raising questions about the potential impact of caprolactam contamination on such high-risk populations.

Surprisingly, limit values for leachables cannot be found in the literature, as they are excluded from ICH guideline Q3B (“Impurities in new drug product”), but ICH is currently working on ICH Q3E (“Guideline for Extractables and Leachables”).

A wide variety of organic and inorganic substances with various toxicity levels have been grouped under the “leachables” denomination. Among these, caprolactam is certainly not the most toxic, but its presence in NS and D5W in the mg/L range appears problematic. In the literature, similar work was conducted on NS PVC bags¹⁸ and found levels in the µg/L range for several leachables, such as phthalides (16-580 µg/L), bisphenol A (320 µg/L), mono(2-ethylhexyl)-phthalate (454 µg/L) and di(2-ethylhexyl)-phthalate (DEHP) (5-7 µg/L). Only cyclohexanone was found in the mg/L range (35 mg/L). PVC leachables contamination has been widely described, and its implication was clinically evaluated, for example, in pediatric practice for the most toxic substances such as DEHP^{19,20} but also for the most concentrated such as cyclohexanone.²¹ It is disturbing that such studies may have been carried out but not published for caprolactam.

Toxicological studies on caprolactam have been described for pulmonary or cutaneous exposure, as workers may be exposed during nylon production. It has been described as an irritating agent for skin and mucosa.²² Few animal studies have also been described for oral administration. In subchronic feeding studies in rats, nephropathies and mild liver weight increases were described.²³ Such effects were not found in dog studies.²⁴ Therefore, caprolactam is not considered to be particularly toxic via the oral route of exposure, and a “derived no effect level” of 8.55 mg/kg/day for long-term oral exposure has been proposed.²² However, parenteral evaluations are lacking. We hope that unpublished toxicological data exist and have been used to define a caprolactam safe level. Therefore, in clinical practice, without any information on caprolactam toxicity and pharmacokinetics, it is

reasonable to wonder whether such plastic bags can be used in neonates, pregnant women, patients with renal/hepatic insufficiencies, or any other high-risk population. To our knowledge, physical or chemical incompatibilities between caprolactam and drugs have not been described. In this study, we did not find evidence of incompatibility between caprolactam and cisplatin.

In our view, toxicological data on leachables and other impurities are as important as clinical studies in proving the safety of a drug and cannot be covered by industrial secrecy. We recommend improving transparency by systematically publishing the toxicological studies carried out by the pharmaceutical industry. Limit values for leachables and also for all impurities should also be published. Finally, as leachables may give rise to pharmacological or physicochemical interactions, their presence should be detailed when they are not just found at trace levels.

Conclusion

Plastic containers suffer from leachables contamination, whatever the type of polymeric material they contain. Herein, we have described a leachable of nylon material, caprolactam, found in NS- and D5W-containing infusion bags, with mean (SD) caprolactam content ranging from 5.43 (0.21) to 22.83 (1.26) mg/L. This contamination results in an administration per NS or D5W container of 1.11 to 5.49 mg of caprolactam. Lower container volumes are associated with higher caprolactam concentrations.

Caprolactam concentrations were stable over time in untouched bags, whatever the storage conditions, but in bags containing caprolactam-free NS, caprolactam concentrations slightly increased over 6 months with storage at 40 °C and 75% RH. Moreover, varying the pH seemed to have little or no influence on the caprolactam content in NS plastic bags.

Finally, a mixture of caprolactam-contaminated NS and a highly reactive drug (cisplatin) had no influence on caprolactam content, which is reassuring with regard to potential physicochemical interactions of caprolactam with drugs.

However, in the absence of information it is appropriate to consider whether such caprolactam-contaminated plastic bags are the safest alternative for patients, particularly in pediatric practice (including parenteral nutrition) and for pregnant women.

Disclosures

The authors have declared no potential conflicts of interest.

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References

1. Czuba L. Application of plastics in medical devices and equipment. In: Modjarrad K, Ebnesajjad S, eds. *Plastics Design Library, Handbook of Polymer Applications in Medicine and Medical Devices*. William Andrew Publishing; 2014:9-19.
2. Cuadros-Rodríguez L, Lazúen-Muros M, Ruiz-Samblás C, Navas-Iglesias N. Leachables from plastic materials in contact with drugs. State of the art and review of current analytical approaches. *Int J Pharm*. 2020;583:119332.
3. Kerr DIB, Dennis BJ, Breuker ELM, Prager RH, Ward AD, Duong T. Antagonism of GABA-mediated inhibition in the central nervous system by caprolactam derivatives. *Brain Res*. 1976;110:413-416.
4. Kerr DI, Ong J, Prager RH, Ward DA. Caprolactam-barbiturate interaction at the GABAA receptor complex in the guinea-pig intestine. *Eur J Pharmacol*. 1986;124:203-206.
5. Gross P. Biologic activity of epsilon-caprolactam. *Crit Rev Toxicol*. 1984;13:205-216.
6. Jenke D. Safety risk categorization of organic extractables associated with polymers used in packaging, delivery and manufacturing systems for parenteral drug products. *Pharm Res*. 2015;32:1105-1127.
7. Florence A, Attwood D. Physicochemical drug interactions and incompatibilities. In: *Physicochemical Principles of Pharmacy*. Springer; 1998:449-492.
8. Le Quinio P, Beiler B, Lider P, Demoré B, Vigneron J. Quality control of cytotoxic infusions disturbed by a change of infusion bag: a case report. *Eur J Oncol Pharm*. 2019;2:16. doi:10.1097/OP9.000000000000016
9. Desideri I, Aiello F, Giannotti S, et al. Are commercially multi-dose formulations the best solution ? A spectroscopical quality study of cyclophosphamide. *Eur J Hosp Pharm*. 2016;23:A206-A207. doi:10.1136/ejhpharm-2016-000875.467

10. Fisher WB, Crescentini L. Polyamides (caprolactam) In: *ECT*. 3rd ed, vol. 18. Allied Chemical Corp.:425-436.
11. Cuiban F, Bolocan I, Barbu E. N-substituted derivatives of ϵ -caprolactam and their thermal and chemical behavior. *ARKIVOC*. 2002;2:56-63A.
12. Bisz E, Podchorodecka P, Szostak M. N-methylcaprolactam as a dipolar aprotic solvent for iron catalyzed cross-coupling reactions: matching efficiency with safer reaction media. *ChemCatChem*. 2019;11:1196.
13. Benson RE, Cairns TL. Chemical reactions of caprolactam. *J Am Chem Soc*. 1948;70:2115-2118.
14. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Dimethyl sulfate. In: *Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide*. International Agency for Research on Cancer; 1999. Accessed August 28, 2023. <https://www.ncbi.nlm.nih.gov/books/NBK498845/>
15. Liu Y, Vinje J, Pacifico C, Natile G, Sletten E. Formation of adenine–N3/guanine–N7 cross-link in the reaction of trans-oriented platinum substrates with dinucleotides. *J Am Chem Soc*. 2002;124:12854-12862.
16. Jenke D, Poss M, Sadain S, Story J, Smith W, Reiber D. Identification of caprolactam oligomers and related compounds in aqueous extracts of nylon-6. *J Appl Polym Sci*. 2005;95:1262-1274.
17. Sarbach C, Yagoubi N, Sauzies J, Renaux C, Ferrier D, Postaire E. Migration of impurities from a multilayer plastics container into a parenteral infusion fluid. *Int J Pharm*. 1996;140:169-174.

18. Arbin A, Jacobsson S, Hänninen K, Hagman A, Östelius J. Studies on contamination of intravenous solutions from PVC-bags with dynamic headspace GC-MS and LC-diode array techniques. *Int J Pharm.* 1986;28:211-218.
19. Kambia K, Dine T, Gressier B, et al. Evaluation of childhood exposure to di(2-ethylhexyl) phthalate from perfusion kits during long-term parenteral nutrition. *Int J Pharm.* 2003;262:83-91. doi:10.1016/s0378-5173(03)00335-1
20. Latini G, Ferri M, Chiellini F. Materials degradation in PVC medical devices, DEHP leaching and neonatal outcomes. *Curr Med Chem.* 2010;17:2979-2989.
21. Bembea MM, Ng DK, Carroll M, et al. Cyclohexanone exposure in children on extracorporeal membrane oxygenation support. *ASAIO J.* 2022;68:419-425.
22. European Chemical Agency. ϵ -caprolactam toxicological summary. Accessed September 1, 2023. <https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/15939/7/1>
23. US Environmental Protection Agency. *Health and Environmental Effects Profile for Caprolactam*. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, US Environmental Protection Agency; 1988.
24. Office of Environmental Health Hazard Assessment, US Environmental Protection Agency. Caprolactam monograph. Accessed August 28, 2023. <https://oehha.ca.gov/media/downloads/cnr/caprolactam2013.pdf>

Disclosures

The authors have declared no potential conflicts of interest.

Key Points

- A cyclic amide leachable (caprolactam) was identified and quantified in some test samples of multilayer plastic infusion bags containing normal saline and 5% dextrose in water.
- Mean (SD) caprolactam levels ranged from 5.43 (0.21) mg/L to 22.83 (1.26) mg/L and did not significantly vary with storage time, whatever the storage conditions.
- Published toxicological studies on parenteral exposure to caprolactam are lacking.

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Table 1. Interlaboratory Results of Testing for Caprolactam Contamination of NS Stored in Infusion Bags

Volume	Origin	Batch	Caprolactam content, mean (SD), mg/L			Mean	% difference L1/L2	S_L^2	S_R	E_N	
			L1	L2	L1					L2	
50 mL	L1	23D16G62	23.71 (0.01)	23.86 (0.03)	23.79	0.66	1.23×10^{-2}	0.11	0.86	0.86	
	L1	23B13G63	24.51 (0.03)	24.73 (0.09)	24.62	0.86	2.16×10^{-2}	0.16	0.84	0.84	
	L1	23E14G60	21.30 (0.01)	21.34 (0.07)	21.32	0.20	4.31×10^{-4}	0.04	0.79	0.79	
	L2	23E15G60	21.57 (0.02)	22.00 (0.10)	21.79	1.95	9.09×10^{-2}	0.31	0.86	0.86	
	L2	22L22G63	22.43 (0.02)	22.80 (0.02)	22.61	1.65	7.05×10^{-2}	0.27	0.86	0.86	
100 mL	L1	23A11G61	14.96 (0.01)	14.93 (0.04)	14.94	-0.20	2.64×10^{-4}	0.03	0.81	0.81	
	L1	23B21G62	15.32 (0.06)	15.45 (0.11)	15.38	0.82	5.66×10^{-3}	0.11	0.65	0.65	
	L1	23D06G62	14.86 (0.02)	14.87 (0.01)	14.87	0.03	0	0.01	0.09	0.09	
	L2	22H27G61	14.21 (0.01)	14.30 (0.05)	14.25	0.65	4.09×10^{-3}	0.07	0.86	0.86	
250 mL	L1	23D12E4B	10.31 (0.01)	10.20 (0.03)	10.26	-1.08	5.93×10^{-3}	0.08	0.85	0.85	
	L1	23B25E3T	10.78 (0.02)	10.76 (0.03)	10.77	-0.24	1.94×10^{-4}	0.03	0.56	0.56	
	L1	23E05E4L	10.16 (0.02)	10.13 (0.04)	10.15	-0.35	3.92×10^{-4}	0.03	0.66	0.66	
	L2	23F12E4Z	10.26 (0.00)	10.37 (0.01)	10.32	1.10	6.48×10^{-3}	0.08	0.87	0.87	
500 mL	L1	23D10E7G	8.47 (0.01)	8.44 (0.07)	8.45	-0.35	0	0.04	0.68	0.68	
	L1	23C01E7T	8.66 (0.01)	8.60 (0.03)	8.63	-0.62	1.33×10^{-3}	0.04	0.85	0.85	
	L1	23E11E7C	8.21 (0.01)	8.15 (0.01)	8.18	-0.82	2.22×10^{-3}	0.05	0.85	0.85	
	L2	23E11E7C	7.97 (0.03)	7.89 (0.07)	7.93	-1.01	2.33×10^{-3}	0.07	0.68	0.68	
	L2	23D25E7K	8.52 (0.02)	8.45 (0.09)	8.48	-0.92	2.05×10^{-3}	0.07	0.81	0.81	
1,000 mL	L1	22K19E0J	5.64 (0.01)	5.43 (0.02)	5.53	-3.81	2.14×10^{-2}	0.15	0.86	0.86	

L1	22F17T2F	5.68 (0.01)	5.52 (0.02)	5.60	-2.94	1.31 $\times 10^{-2}$	0.12	0.86	0.86
L1	23A26E7U	5.54 (0.00)	5.45 (0.02)	5.49	-1.68	4.14 $\times 10^{-3}$	0.07	0.87	0.87
L1	23D18E0C	5.53 (0.02)	5.38 (0.03)	5.46	-2.76	1.09 $\times 10^{-2}$	0.11	0.85	0.85
L2	23C25E9G	5.44 (0.03)	5.29 (0.03)	5.36	-2.81	1.08 $\times 10^{-2}$	0.11	0.82	0.82

Abbreviations: L1, laboratory 1; L2, laboratory 2; S_L^2 = intralaboratory variance; S_R = interlaboratory reproducibility standard deviation; E_N = normalized deviation; NS, normal saline.

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Table 2. Interlaboratory Results of Testing for Contamination of Solutions of Caprolactam and D5W Stored in Infusion Bags

Volume	Origin	Batch	Caprolactam content, mean (SD), mg/L			Mean	% difference L1/L2	S_L^2	S_R	E_N	
			L1	L2	L1					L2	
50 mL	L1	23A06G63	22.79 (0.01)	23.11 (0.05)	22.95	1.39	5.10×10^{-2}	0.23	0.86	0.86	
	L1	23A06G63	22.15 (0.03)	22.48 (0.05)	22.32	1.48	5.48×10^{-2}	0.24	0.86	0.86	
	L1	23A06G63	22.17 (0.01)	22.49 (0.09)	22.33	1.41	4.91×10^{-2}	0.23	0.86	0.86	
	L2	23F09G63	20.76 (0.01)	21.92 (0.10)	21.34	5.30	6.73×10^{-1}	0.82	0.87	0.87	
100 mL	L1	22G20G62	16.61 (0.03)	16.94 (0.02)	16.78	1.95	5.45×10^{-2}	0.23	0.86	0.86	
	L1	22G20G62	13.64 (0.02)	13.76 (0.03)	13.70	0.82	6.24×10^{-3}	0.08	0.84	0.84	
	L1	23A30G62	16.18 (0.01)	16.37 (0.02)	16.28	1.16	1.80×10^{-2}	0.13	0.86	0.86	
	L2	22F24G62	14.54 (0.02)	14.95 (0.09)	14.74	2.76	8.38×10^{-2}	0.29	0.86	0.86	
	L2	23D15G61	14.83 (0.02)	15.29 (0.07)	15.06	2.96	1.02×10^{-1}	0.32	0.86	0.86	
250 mL	L1	22K10EAT	10.63 (0.00)	10.63 (0.05)	10.63	-0.03	0	0.02	0.87	0.87	
	L1	23B11E4A	10.25 (0.01)	10.33 (0.05)	10.29	0.77	2.89×10^{-3}	0.06	0.84	0.84	
	L1	23A13E4U	10.35 (0.01)	10.56 (0.05)	10.46	2.03	2.26×10^{-2}	0.15	0.86	0.86	
	L1	23H11E4V	9.33 (0.01)	9.39 (0.04)	9.36	0.66	1.76×10^{-3}	0.05	0.85	0.85	
	L2	22K10EAT	10.05 (0.01)	10.15 (0.02)	10.10	0.98	4.86×10^{-3}	0.07	0.84	0.84	
	L2	25E15E4D	9.90 (0.00)	10.05 (0.04)	9.98	1.52	1.15×10^{-2}	0.11	0.87	0.87	
500 mL	L1	22K16E8L	8.32 (0.00)	8.40 (0.01)	8.36	0.99	3.46×10^{-3}	0.06	0.87	0.87	
	L1	23B14E3E	8.38 (0.01)	8.40 (0.05)	8.39	0.32	1.15×10^{-4}	0.03	0.80	0.80	
	L1	22L20E3L	7.31 (0.01)	7.45 (0.01)	7.38	1.89	9.89×10^{-3}	0.10	0.86	0.86	
	L1	23C18E1J	8.41 (0.01)	8.42 (0.05)	8.41	0.02	0	0.02	0.12	0.12	
	L2	23A23E3M	8.34 (0.00)	8.42 (0.05)	8.38	0.94	2.94×10^{-3}	0.06	0.87	0.87	
1,000 mL	L1	23C16E2A	5.41 (0.01)	5.50 (0.03)	5.46	1.66	4.09×10^{-3}	0.07	0.86	0.86	
	L1	22J18E2C	5.45 (0.01)	5.47 (0.03)	5.46	0.27	1.32×10^{-3}	0.02	0.69	0.69	

L1	23A30E2B	5.73 (0.01)	5.68 (0.06)	5.71	-0.86	8.24×10^{-5}	0.04	0.84	0.84
L1	23A31E2D	5.58 (0.01)	5.58 (0.02)	5.58	0.01	0×10^{-4}	0.01	0.02	0.02
L2	22C18T3H	5.08 (0.01)	5.10 (0.08)	5.09	0.24	0	0.04	0.63	0.63
L2	22L12E2Z	5.29 (0.01)	5.27 (0.02)	5.28	-0.30	5.81×10^{-5}	0.02	0.70	0.70

Abbreviations: L1, laboratory 1; L2, laboratory 2; S_L^2 = intralaboratory variance; S_R = interlaboratory reproducibility standard deviation; E_N = normalized deviation; NS, normal saline.

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Table 3. Mean Caprolactam Content and Theoretical Maximal Daily Dose Administered

Diluent and container size	Caprolactam content, mean (SD) global value, mg/L	Mean caprolactam content per container, mg	Total maximal daily dose of caprolactam administered to patient, mg
NS 50 mL	22.83 (1.26)	1.14	68.5
NS 100 mL	14.86 (0.42)	1.49	44.6
NS 250 mL	10.37 (0.25)	2.59	31.1
NS 500 mL	8.34 (0.26)	4.17	25.0
NS 1,000 mL	5.49 (0.11)	5.49	16.5
D5W 50 mL	22.23 (0.68)	1.11	66.7
D5W 100 mL	15.31 (1.13)	1.53	45.9
D5W 250 mL	10.14 (0.42)	2.53	30.4
D5W 500 mL	8.19 (0.41)	4.09	24.6
D5W 1,000 mL	5.43 (0.21)	5.43	16.3

Abbreviations: D5W, 5% dextrose in water; NS, normal saline.

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Table 4. Influence of pH on Caprolactam Content

pH	Caprolactam content at day 0, mg/L	Caprolactam content at day 15, mg/L
2	14.96	14.69
4	14.80	14.91
6	15.12	15.20
8	14.66	14.98
10	14.71	14.76

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