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Research Article

Quality of the fibrinogen index in freeze-dried plasma for external blood coagulation testing programs

Calidad del índice de fibrinógeno en plasma liofilizado para programas de pruebas externas de coagulación sanguínea

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ABSTRACT

Background: Lyophilized plasma is widely used in external quality assessment for fibrinogen testing, where sample homogeneity and stability are critical. This study evaluated these factors, addressing challenges in sample preparation to enhance the quality of medical services.

Objective: To assess the homogeneity and stability of fibrinogen in lyophilized plasma according to ISO 13528:2022 and ISO Guide 35:2010 standards.

Methods: The study utilized experimental freeze-dried control samples containing fibrinogen. Random sampling was performed using Microsoft Excel 16, and one-way ANOVA was applied to assess sample


2025;54(3):e025076349

homogeneity. Stability at different time points and temperatures was evaluated using t-tests. Key variables included: Mean (central tendency), Standard Deviation (data dispersion), Homogeneity (consistency within a batch, assessed via P-values), and Stability (maintenance of values over time under varied storage conditions).

Results: The fibrinogen values of the standard samples demonstrated good homogeneity (p= 0.890> 0.05). Freeze-dried samples stored at 2–8°C remained stable over 5 months, with t-test p-values of 0.114, 0.242, and 0.391, all > 0.05. Samples stored at –20°C were stable over 3 months (p= 0.520, 0.761, and 0.353). Additionally, short-term stability assessments on days 1, 3, 5, and 7 yielded p-values of 0.093, 0.742, 0.057, and 0.270, respectively, indicating no significant changes and confirming overall stability.

Conclusion: Lyophilized plasma containing the fibrinogen index is both homogeneous and stable when stored at 2-8°C and -20°C, as well as during transportation. These significant findings pave the way for further research and potential advancements in coagulation testing.

Keywords: coagulation; quality assurance; fibrinogen; lyophilized; plasma.

RESUMEN

Antecedentes: El plasma liofilizado se utiliza en la evaluación externa de la calidad de las pruebas de fibrinógeno, pues homogeneidad y estabilidad de la muestra son fundamentales.

Objetivo: Evaluar la homogeneidad y estabilidad del fibrinógeno en plasma liofilizado, según las normas ISO 13528:2022 e ISO Guía 35:2010.

Métodos: Se utilizaron muestras de control experimentales liofilizadas con fibrinógeno. Se realizó muestreo aleatorio y se aplicó ANOVA de una vía para evaluar homogeneidad. La estabilidad en diferentes momentos y temperaturas se evaluó mediante pruebas t. Las variables fueron: media, desviación estándar, homogeneidad (consistencia dentro de un lote, evaluada mediante valores p) y estabilidad (mantenimiento de los valores a lo largo del tiempo en diversas condiciones de almacenamiento).

Resultados: Los valores de fibrinógeno de las muestras estándar mostraron buena homogeneidad (p= 0,890> 0,05). Las muestras liofilizadas almacenadas a 2–8 °C se mantuvieron estables durante 5


2025;54(3):e025076349

meses (prueba t con p= 0,114, 0,242 y 0,391; todos > 0,05). Las muestras almacenadas a –20 °C se mantuvieron estables durante 3 meses (p= 0,520, 0,761 y 0,353). Las evaluaciones de estabilidad a corto plazo, realizadas los días 1, 3, 5 y 7 arrojaron valores p= 0,093, 0,742, 0,057 y 0,270, respectivamente, lo que no indicó cambios significativos y confirmó la estabilidad general.

Conclusión: El plasma liofilizado con índice de fibrinógeno es homogéneo y estable, tanto al almacenarse a 2-8 °C, como a -20 °C, y durante el transporte. Estos hallazgos abren el camino a futuras investigaciones y posibles avances en las pruebas de coagulación.

Palabras clave: coagulación; evaluación externa de calidad; fibrinógeno; liofilizado; plasma.

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INTRODUCTION

Anemia, caused by factors like alcohol use, sickle cell disease, thalassemia, chronic disease, iron deficiency, and lead poisoning, occurs when the body lacks essential nutrients to produce red blood cells. This impairs oxygen transport, hindering recovery and increasing infection risk.[1,2] Zinc deficiency is known to have a significant impact on the immune system and various physiological functions.[3] A study by *La Qui Phu* et al. reported a significantly higher rate of anemia in children with pneumonia and zinc deficiency (37%) compared to those without zinc deficiency (19.3%) ($p< 0.05$).[4] This predisposes patients with pneumonia to complications, weakens the immune system, and increases the risk of developing coagulation disorders.[2] The fibrinogen test is a crucial tool in assessing clotting ability and monitoring risks associated with bleeding, clotting, and various conditions such as cardiovascular or liver disease.[5]

Lyophilized plasma is processed and dried for use as a reference sample in external quality control programs to ensure the accuracy and stability of test results. Quality control testing is essential in laboratories to guarantee precise results across various testing platforms.[6] Studies have explored


2025;54(3):e025076349

lyophilized plasma, especially fibrinogen concentrates, in various medical settings. Clinical trials have compared fibrinogen concentrate to cryoprecipitate in severe trauma patients.[7] *Garrick M.* et al.[8] conducted a study comparing French lyophilized plasma with fresh frozen plasma and found that French lyophilized plasma achieved higher fibrinogen concentrations. The impact of lyophilization on fibrinogen's coagulation properties is important when calibrating assays with lyophilized plasma. This is crucial in managing major bleeding, where liquid plasma ensures higher plasma levels and accurate coagulation tests.[9] Research on the effects of freeze-drying, freezing, and cryopreservation on plasma components, particularly fibrinogen, has yielded mixed results. Freeze-dried plasma was found to have lower fibrin content compared to fresh plasma, while freezing and freeze-drying were shown to alter the activity of fibrinogen.[10] Despite the limited research supporting the use of fibrinogen concentrate over traditional sources, its potential benefits in managing coagulopathy, particularly in trauma-induced cases, are being recognized.[11]

Lyophilized plasma samples are essential in external quality assurance programs to ensure accurate and consistent fibrinogen assay results for reliable disease diagnosis and treatment.[12] Lyophilized plasma is a valuable tool in supporting lab quality assurance. Quality control products play a crucial role in ensuring precise and accurate results in clinical diagnostics labs.[13]

Laboratory results can be enhanced through rigorous internal control procedures and participation in external quality assessment programs, which help address these challenges. Comparisons between laboratories are crucial for identifying analytical errors not detected by internal controls.[14] So The objective of this research is to investigate the homogeneity and stability of the fibrinogen index in lyophilized plasma, by ISO 13528:2022 and ISO Guide 35:2010 standards.


2025;54(3):e025076349

METHODS

Research method: Experimental research.

Research period: January 2022 to June 2024.

Sampling criteria: Fresh frozen plasma samples, within their expiry date and meeting blood transfusion safety standards as per Circular No. 26/2013/TT-BYT.[15] This circular outlines professional and technical activities related to blood transfusion, including donor selection, blood collection, testing, processing, storage, transportation, management, and use of blood products for treatment; it also covers risk monitoring in blood transfusion, the blood transfusion council at healthcare facilities, and record-keeping and reporting procedures.[15] Fibrinogen analysis results in the sample were less than 4 g/L.

Exclusion criteria: Samples with temperature instability during storage that do not meet the selection criteria.

Steps to follow (Fig. 1)

Thaw fresh frozen plasma completely within one hour at room temperature.

Add the preservative mixture and mix thoroughly using a magnetic stirrer in a thermostatically controlled bath for 30 minutes.

Filter the plasma solutions through a 0.22 mm filter paper into a wide-mouth flask. Determine the fibrinogen value in plasma using the Sysmex CS-2000i automatic coagulation system. The system, from Sysmex, Japan, utilizes a multi-wavelength optical measurement method with the following reagents: Actin FSL, LOT: 562674; Calcium Chloride, LOT: 563883; Dade Innovation, LOT: 549783A; Dade Thrombin Reagent, LOT: 565131; Owren's Veronal Buffer, LOT: 569915; CA Clean I, LOT: A1127; CA Clean II, LOT: A1221. Quality control materials include Dade Ci-Trol 1, LOT: 548517 and Dade Ci-Trol 2, LOT: 564845.

Adjust to create a sample set with typical fibrinogen values according to the reagent lot used.

Dispense 1 mL of plasma into a 3ml brown vial and refrigerate at -80°C for at least 24 hours, then freeze-dry according to the lyophilization procedure at the control center and per the manufacturer's instructions.

Assess homogeneity by randomly selecting ten vials from 200 samples each lot of lyophilized samples at each analysis level, recording, and analyzing using a one-way ANOVA test.

2025;54(3):e025076349

After freezing the batch of samples, evaluate their stability at different stages and temperature milestones. Assess shipping stability over 1, 3, 5, and 7 days and storage stability over 1, 3, and 5 months. Three samples were selected randomly for each stage for evaluation to test the fibrinogen value compared with the initial value using a t-test.

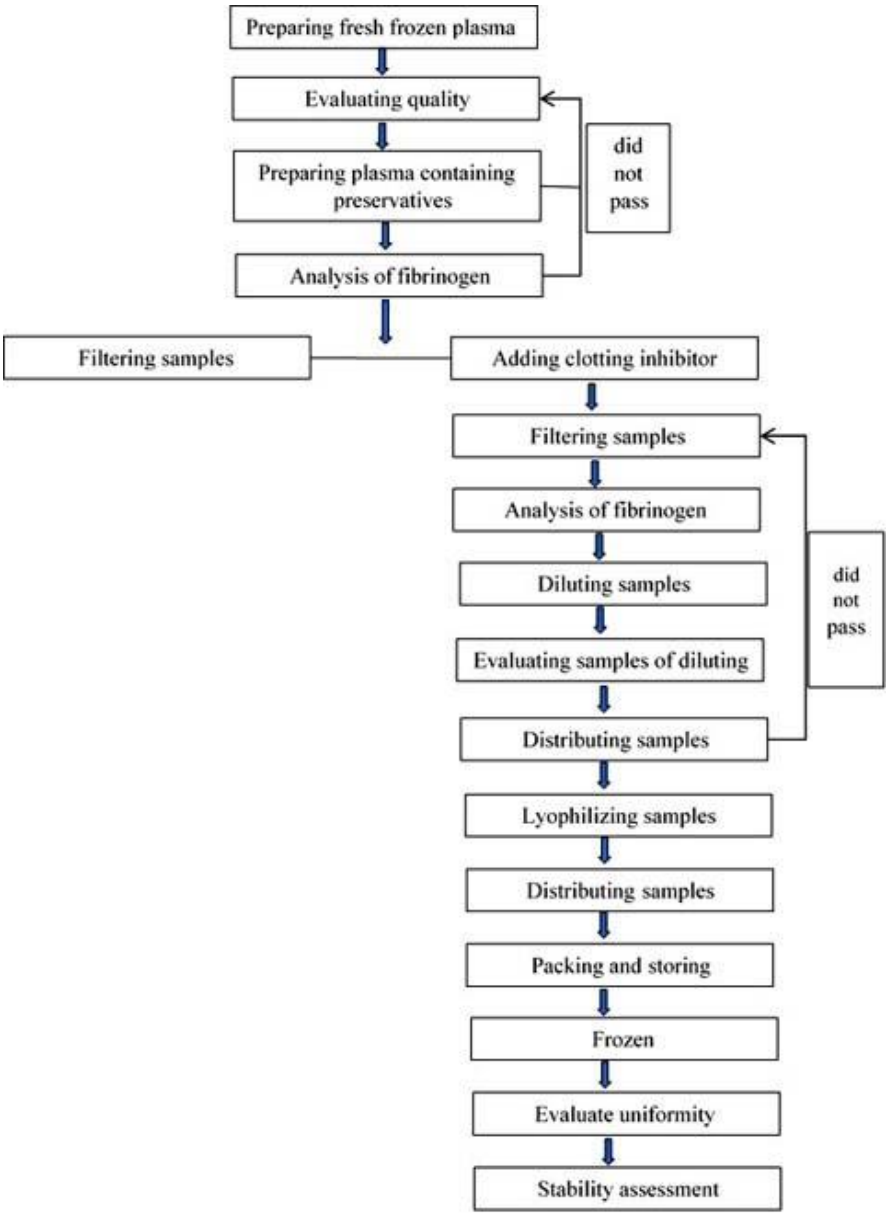

Fig. 1 - Diagram of the sample production process and evaluation of lyophilized plasma samples.


2025;54(3):e025076349

After the lyophilized plasma sets were distributed and packaged, homogeneity assessment was performed by randomly selecting ten vials from each batch, reconstituting them with distilled water, and analyzing each vial twice using the Sysmex CS2000i automatic coagulation system. Subsequently, Excel software was used to conduct one-way ANOVA to evaluate the uniformity of the fibrinogen index in lyophilized plasma.

Once the sample set was confirmed to be homogeneous, its stability was evaluated during transportation and storage using Stata 14.1 software to perform t-tests. These tests assess the stability of the fibrinogen index in lyophilized plasma at a 95% confidence level. A sample was considered stable during storage if the *p* value> 0.05 (p< 0.05 meaning not stable sample). Then the fibrinogen levels at the time of evaluation with the initial homogenization analysis data were compared.

The effects of different storage conditions on raw materials from fresh frozen plasma, stored at -20°C or lower were scanning up to 6 months to ensure sample properties closely resembled plasma. Fresh frozen plasma was selected as the sample source to minimize interference and meet external research requirements.

According to ISO 13528:2022,[16] the proficiency testing provider must ensure that the proficiency testing lots are sufficiently homogeneous and stable to meet the objectives of the proficiency testing program. The study demonstrated that the sample lots achieved uniformity consistent with the one-way ANOVA test method, *p*> 0.05.

For the standards of external control samples: It is mandatory that samples in the same batch not only be uniform but also maintain the stability of external control parameters over time and across storage temperatures.

Data analysis

Using excel software to conduct one-way ANOVA for evaluating the uniformity of the fibrinogen index in lyophilized plasma and Stata 14.1 to perform t-tests to assess the stability of the fibrinogen index in lyophilized plasma.[17] The t-test was performed on the variable is stability.


2025;54(3):e025076349

Ethical considerations

This study adhered to the ethical standards established by national research committees and organizations, following the principles outlined in the 2024 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. The Biomedical Research Ethics approved the study (approval number 150/HDDD, dated January 17, 2022). Consent was obtained from all blood donors prior to their participation in the study. All donor information was kept confidential, their health was safeguarded, and their mental well-being was not adversely affected.

RESULTS

The results of the homogeneity assessment of plasma after freeze-drying are presented in table 1. This table shows the mean values from two runs (two independently repeated analytical methods) for samples 1, 2, and 3. The p-value, calculated using a one-way ANOVA test, along with the mean and standard deviation (SD), is also provided. According to table 1, the homogeneity of the samples was assessed using a one-way ANOVA test at a significance level of $\alpha = 0.05$. The fibrinogen values of the standard samples demonstrated homogeneity with $p > 0.05$ -specifically, $p = 0.890$- indicating that the required level of uniformity was achieved.


2025;54(3):e025076349

Table 1 - Results of homogeneity assessment of average fibrinogen levels in sample lots after freeze-drying (g/L)

Sample bottle	Normal level		
	Lot 1	Lot 2	Lot 3
1	2.50	2.53	2.56
2	2.52	2.53	2.54
3	2.58	2.56	2.53
4	2.61	2.57	2.60
5	2.60	2.63	2.59
6	2.55	2.56	2.62
7	2.54	2.55	2.51
8	2.62	2.65	2.62
9	2.61	2.60	2.59
10	2.61	2.49	2.60
Mean	2.57	2.57	2.58
Mean (Lot 1, Lot 2, Lot 3)	2.58		
SD	0.04		
P-value	0.890 (*)		
Homogeneous *p> 0.05*	Obtain		

(*) one-way ANOVA test.

The stability assessment of lyophilized plasma samples containing fibrinogen demonstrated consistent results under both refrigerated and frozen storage, as well as during simulated transport conditions.

- Storage Stability: At 2–8°C, fibrinogen concentrations remained stable throughout a 5-month storage period. All t-test comparisons with baseline values yielded non-significant differences (p= 0.114, 0.242, 0.391), confirming no meaningful degradation over time. Similarly, storage at -20°C showed excellent preservation of fibrinogen for up to 5 months. T-test results at 1, 3, and 5 months (p= 0.520, 0.761, 0.353) indicated high consistency with initial concentrations, reaffirming suitability for long-term frozen storage.
- Transport Stability: Simulated transport testing revealed that fibrinogen values remained within acceptable limits up to 7 days, with no statistically significant deviations from baseline at any time


2025;54(3):e025076349

point (p= 0.093, 0.742, 0.057, 0.270). These findings support the use of lyophilized fibrinogen samples in external quality assessment (EQA) programs, ensuring reliable performance during routine transport durations.

Conclusion: Lyophilized samples exhibit robust short-term transport stability and long-term storage stability under both refrigeration and freezing conditions, making them suitable for distribution and usage in external quality control schemes involving fibrinogen assays.

DISCUSSION

Introduced in 1991, Methylene Blue (MB) was the first method developed to inactivate pathogens in labile blood components. MB combined with light (MBL) is capable of inactivating most viruses.[18] However, there is substantial evidence that coagulation factors in plasma, particularly factor VIII, are adversely affected by MB during processing. Consequently, MB was not selected as a preservative or disinfectant.[19] Other reports have indicated that Amotosalen can effectively inactivate pathogens in plasma and maintain coagulation factors, with an average activity level of 81% to 97%.[6,20] Nevertheless, the complexity of the Amotosalen treatment process and the specialized equipment required make it unsuitable for authors Center's conditions.

When investigating the quality of freeze-dried plasma samples, *Mok G* et al.[21] observed that the freeze-drying process mainly affected FVIII and vWF/RiCoF, which decreased by more than 10% compared to pre-freeze-drying levels, while fibrinogen and other coagulation factors remained relatively stable.[21] The findings are consistent with those of *Mok G* et al.;[21] in this research on freeze-dried samples, fibrinogen levels remained virtually unchanged, with a percentage difference of only 0.5%.

The freeze-drying process itself can affect plasma samples. Additionally, a common challenge in processing freeze-dried samples is the skill required for reconstitution, which demands meticulous and highly accurate techniques.[22]

When studying the quality of freeze-dried plasma samples, Bux J et al.[23] found that the freeze-drying process only affected FVIII and vWF/RiCoF (decreased by more than 10% compared to before freeze-


2025;54(3):e025076349

drying), while fibrinogen and some other coagulation factors remained relatively stable. This study assessed the homogeneity of freeze-dried plasma samples using a single-factor ANOVA test at $\alpha = 0.05$. The fibrinogen values demonstrated sufficient homogeneity, with a p value > 0.05, specifically $p = 0.890$.

Evaluation of storage stability of sample sets

In the study by *Woodhams B.* et al.,[24] different storage temperatures were shown to affect the stability duration of samples. At -24°C, the stability of the coagulation factor fibrinogen can extend up to 12 months, and up to 24 months at -70°C. It is evident that fibrinogen's stability duration increases with lower storage temperatures. Therefore, storing ordinary plasma preparations after dilution at -80°C to ensure stability before lyophilization.

Additionally, in another study, a paper-based lateral flow device was utilized to measure fibrinogen levels in lyophilized plasma, further underscoring the potential applications of lyophilized plasma in research and clinical settings.[25] Commercial fibrinogen concentrates, derived from pooled human plasma through cryoprecipitation, are routinely used in clinical settings.[26] These concentrates, which contain lyophilized plasma, can be reconstituted for various uses. Due to *Merivaara A* et al.,[27] discusses the use of lyophilized plasma in significant trauma scenarios, highlighting its capability to maintain fibrinogen levels and potentially supplement therapeutic plasma or cryoprecipitate. Lyophilization, also known as freeze-drying, is a widely studied method for preserving biological materials and cells.[28] Lyophilized plasma, especially as fibrinogen concentrates, shows potential for applications in trauma treatment, medical research, and biological material preservation. Further research could lead to significant advancements in healthcare and biotechnology.

Saidykhan J et al.[25] studied the stability of lyophilized plasma samples over 12 months at temperatures of 4°C, 25°C, and 40°C, evaluated at 6 and 12 months. The results revealed that fibrinogen concentrations in samples stored at 4°C and 25°C significantly decreased after six months, with p values of 0.04 and 0.02, respectively. The stability was notably lower at 40°C, with $p < 0.001$. This is consistent with the study of *Bux J* et al.,[23] which indicated that coagulation factors in lyophilized samples were maintained at normal levels after 24 months of storage at 4°C, suggesting that this temperature is optimal for sample preservation. Similarly, in studies examining the stability of lyophilized plasma at 2-8°C and -20°C, all samples achieved stability over ten weeks at all evaluation points, with *p values* > 0.05.


2025;54(3):e025076349

Saidykhan J et al.[25] suggested that fibrinogen concentration in lyophilized plasma stored at 4°C could be maintained stable for less than six months and was less stable at higher temperatures of 25°C and 40°C.

In this research, samples were assessed for stability at 2-8°C and -20°C over one, three, and five months. Stability was confirmed using t-tests, comparing initial fibrinogen values with those at later intervals. Results showed no significant difference ($p > 0.05$), indicating the samples remained stable for up to 5 months at both temperatures.

Assessment of the transport stability of the sample set

External quality assessment is a crucial component of quality assurance for laboratory hemostasis assays. Lyophilization of plasma provides stability for labile coagulation factors, facilitating the comparison of results across participating centers. However, the stability of lyophilized samples during transport can be affected by high ambient temperatures, particularly in certain geographic regions.[23]

Jennings I et al.[29] examined the stability of lyophilized plasma samples exposed to an average temperature of 31.9°C, reaching a maximum of 39.7°C over a shipping period of 1 to 8 weeks. The findings revealed that over six weeks, the average change in fibrinogen levels was less than 0.5% at 22°C, less than 2.5% at 30°C, and up to 9% at 37°C. When assessed using a one-way ANOVA, the average fibrinogen values at two, four, and six weeks at 22°C, 30°C, and 37°C showed no statistically significant differences, with a $p > 0.05$. These results align with this study, indicating that freeze-dried samples can remain stable within one week when temperatures range from 2°C to 30°C during transportation.

In the study by *Levy JH* et al.[30] the temperature during freeze-drying is critical for preserving fibrinogen. Plasma is frozen at -30°C to -50°C to protect fibrinogen from degradation. However, excessively low or uneven temperatures can alter its structure. During the drying stage, temperatures between -20°C and 0°C under vacuum are used to remove water without damaging fibrinogen. Higher drying temperatures can destabilize it. The freeze-drying process takes 12-24 hours for freezing and 24-48 hours for drying. Insufficient or excessive durations can lead to suboptimal dryness or fibrinogen degradation.

This study demonstrates that lyophilized plasma containing the fibrinogen index is both homogeneous and stable when stored at 2-8°C and -20°C, as well as during transportation based on ISO 13528:2022

and ISO Guide 35:2010 standards. These significant findings pave the way for further research and potential advancements in coagulation testing.

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2025;54(3):e025076349

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Conflicts of interests

The authors declare that they have no competing interests.

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Authors' contribution

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2025;54(3):e025076349

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Data Availability

This research data is confidential according to the applicable confidentiality agreements and regulations and, therefore, cannot be publicly displayed or shared. The data are securely stored at Department of Nursing and Medical Technology, Can Tho University of Medicine and Pharmacy. Access to these data requires proper authorization. If you have any questions or need further information, please contact Vu Quang Huy at drvuquanghuy@gmail.com