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Stability Study for Determining the Shelf Life of Glucosamine Hydrochloride Laboratory Reference Standard

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ABSTRACT / ABSTRAK

Reference standards are essential in drug and food control to ensure the quality and validity of test results. According to ISO 17034:2016, the Center for National Quality Control Laboratory of Drugs and Food (PPPOMN), as a producer of reference materials, must evaluate and monitor the stability of the standards it produces. Stability testing is critical to maintain product quality during storage and use. However, PPPOMN-developed reference standards had not undergone stability testing to determine shelf life. This study therefore conducted a stability assessment of the Glucosamine hydrochloride reference standard to ensure stability during transportation, distribution, and storage. Long-term stability tests were conducted at 4–8°C at 0 months (control), 72 months, and 144 months. Short-term stability tests were performed at 25°C and 60°C for 72, 120, 168, and 240 hours, with 0 hours as the control. Stability analysis was performed using validated High-Performance Liquid Chromatography (HPLC), and analyte stability was assessed using a t-test. Results indicated that the Glucosamine hydrochloride secondary reference standard remained stable under recommended storage conditions for 144 months and at distribution temperatures up to 60°C for 240 hours (t-count = 0.976). These findings demonstrate that the reference standard maintains its quality under specified conditions, ensuring the reliability and validity of pharmaceutical testing. The study concludes that the glucosamine hydrochloride reference standard has guaranteed quality and can be used as long as it is stored under the recommended conditions and shelf life. Information regarding storage conditions and shelf life can be included on the reference standard label.

Baku pembanding sangat penting dalam pengawasan obat dan makanan untuk menjamin kualitas dan validitas hasil pengujian. Sesuai dengan ISO 17034:2016, PPPOMN sebagai produsen bahan acuan harus mengevaluasi dan memonitor stabilitas baku pembanding sekunder yang diproduksi. Uji stabilitas merupakan langkah krusial untuk memastikan bahwa kualitas produk tetap terjaga selama penyimpanan dan penggunaan. Namun, baku pembanding yang dikembangkan oleh PPPOMN belum dilakukan uji stabilitas untuk menentukan masa simpan baku pembanding tersebut. Oleh karena itu, pada penelitian ini dilakukan studi stabilitas baku pembanding glukosamin hidroklorida untuk memastikan kestabilannya selama proses transportasi, distribusi, dan penyimpanan. Studi stabilitas jangka panjang dilakukan pada suhu penyimpanan 4-8°C pada 0 bulan sebagai kontrol dan selama 72 dan 144 bulan, studi stabilitas jangka pendek dilakukan pada suhu 25°C dan 60°C pada 0 jam dan selama 72, 120, 168, dan 240 jam. Metode analisis stabilitas dengan KCKT yang tervalidasi. Stabilitas analit dianalisis dengan uji t. Hasil analisis menunjukkan baku pembanding glukosamin hidroklorida stabil pada suhu penyimpanan yang direkomendasikan selama 144 bulan stabil selama distribusi dengan maksimal suhu 60°C selama 240 jam (t hitung = 0,976). Studi membuktikan

bahwa baku pembanding Glukosamin hidroklorida stabil pada kondisi penyimpanan tersebut. Dengan demikian, kualitas dan validitas hasil pengujian sediaan farmasi yang menggunakan baku pembanding tersebut dapat terjamin. Dari penelitian ini dapat disimpulkan bahwa baku pembanding Glukosamin hidroklorida memiliki kualitas yang terjamin dan dapat digunakan sepanjang disimpan pada kondisi penyimpanan dan umur simpan yang direkomendasikan. Informasi terkait kondisi penyimpanan dan umur simpan dapat dicantumkan pada label baku pembanding tersebut.

;Keywords: stability study, Glucosamine hydrochloride, reference standard, ISO 17034:2016
Kata Kunci: *studi stabilitas, Glukosamin hidroklorida, baku pembanding, ISO 17034:2016*

1. Introduction

Reference standards are uniform and authentic materials used in the testing of physical and chemical properties, whose characteristics are compared with substances of high purity according to their intended use (WHO, 2007). Secondary reference standards are compounds whose characteristics are established through comparison with primary reference standards. Primary reference standards are recognized as having appropriate quality within a specific context, where their values are accepted without comparison to other chemical substances. The traceability of both must be well documented (WHO, 2007).

Secondary reference standards must share the same properties as the relevant primary standards in relation to the designated tests. The requirements for reference standards include clearly defined characteristics, stability, homogeneity, and appropriate labeling on the packaging or certificate of analysis that provides transparent information. The values specified in pharmacopeial reference standards are considered valid for their intended use (ISO, 2009; WHO, 2007).

The development of reference standards is crucial for strengthening testing capacity and capability to enhance drug and food regulatory control in Indonesia. Reference standards are used to ensure the quality and validity of drug and food testing. The Reference Standard Laboratory at the Center for National Quality Control Laboratory of Drugs and Food (PPPOMN), as an ISO 17034-accredited producer of reference materials, is responsible for guaranteeing the quality of both Indonesian Pharmacopeia Reference Standards (BPFI) and Laboratory Reference Standards (BPL). Quality assurance of reference standards is conducted through the evaluation and monitoring of the stability of the standards produced.

Stability testing is a key step in pharmaceutical product development to ensure that quality is maintained throughout storage and use. According to the WHO, environmental factors such as temperature, humidity, and light, as well as product-related factors such as the chemical and physical properties of the active ingredients and excipients, dosage form and composition, manufacturing process, container-closure system, and packaging materials, can all affect the stability of pharmaceutical products (Ashutosh Kumar Yadav et al., 2023). The primary purpose of long-term stability studies is to determine the shelf life of drug products. The term "stability" refers to the length of time a dosage form remains within its specifications before degradation occurs. The shelf life (expiry date) of a product is calculated based on this duration. Stability testing aims to demonstrate how the quality of a drug substance changes over time (Ashutosh Kumar Yadav et al., 2023). Accordingly, this study carried out both long-term and short-term stability testing of the glucosamine

hydrochloride reference standard to verify its stability during transportation, distribution, and storage. The distinction between long-term stability and short-term stability lies primarily in the objectives, observation period, and storage conditions. Long-term stability testing is used to establish expiry dates and recommended storage conditions, typically lasting from six months to several years, depending on the desired shelf life. In contrast, short-term stability testing assesses the stability of a substance when short-term deviations from recommended storage conditions occur, for example, during distribution or temporary removal from storage. The observation period generally ranges from one day to several weeks, depending on the deviation scenario (WHO, 2018).

Glucosamine hydrochloride (CAS 66-84-2), chemically named D-Glucose, 2-amino-2-deoxy-, hydrochloride, is a white or nearly white crystalline powder with the chemical formula C6H13NO5·HCl and a molecular weight of 215.63 g/mol (United States Pharmacopeia, 2023). Its chemical structure is presented in Figure 1.

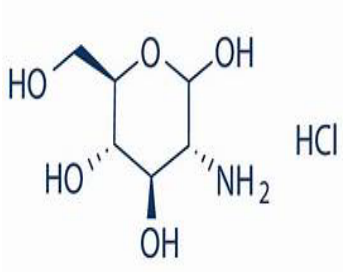

Figure 1. Chemical structure of glucosamine hydrochloride

Glucosamine is an amino sugar naturally produced by the body and serves as a precursor in the biochemical synthesis of glycosylated proteins and lipids. It is a component of polysaccharides, chitosan, and chitin, and is one of the most abundant monosaccharides. Commercially, glucosamine is produced by hydrolyzing the exoskeletons of crustaceans (Nam Xuan Vo, Ngan Nguyen Hoang Le, Trinh Dang Phuong Chu & Khang Xuan An Dinh, Uyen Thi Thuc Che, Thanh Thi Thanh Ngo, 2023). Deficiency in glucosamine can lead to health issues, particularly in joints, increasing the risk of osteoarthritis. Osteoarthritis is a degenerative disease caused by insufficient cartilage regeneration in joints, leading to stiffness, pain, and swelling. Several studies suggest that glucosamine may aid in cartilage regeneration, reduce inflammation, and decrease collagen degradation, thus helping to treat osteoarthritis, although its exact mechanism remains unclear. Glucosamine is most commonly available in supplement form and is widely used as a dietary supplement to promote joint health and manage osteoarthritis.

Several studies have reported methods for analyzing glucosamine hydrochloride using infrared spectrophotometry and high-performance liquid chromatography (HPLC) (Alberto-Silva et al., 2020; Asthana et al., 2019; Choezom et al., 2021). However, no studies have reported stability testing of PPPOMN-produced glucosamine hydrochloride secondary reference standard for shelf-life determination. Therefore, this study conducted stability testing of the glucosamine hydrochloride reference standard to ensure that its quality remains intact during storage and use. The material was characterized using infrared spectrophotometry and HPLC, followed by method validation and stability testing using HPLC. Validation parameters included selectivity, accuracy, linearity, range, detection, and quantification limits, as well as precision (repeatability and intermediate precision).

Consequently, the developed reference standard can be reliably applied in both qualitative and quantitative testing of pharmaceutical and cosmetic products.

2. Methodology

2.1. Time and Place of Study

The study was conducted at the Reference Standard Laboratory, the Center for National Quality Control Laboratory of Drugs and Food (PPPOMN), Indonesian FDA (BPOM).

2.2. Materials and Instruments

The materials used in this study included: Glucosamine hydrochloride USPRS Lot No. F0C363 obtained from USP (Rockville, USA), glucosamine hydrochloride BPL produced by PPPOMN (BPOM, Indonesia) as the sample, potassium bromide, reagents such as sodium pentane sulfonate, HPLC-grade acetonitrile, perchloric acid, potassium hydroxide (Merck, Germany), and demineralized water obtained from a Milli-Q purifier water system (18.2 MΩcm). The instruments used were: a Mettler Toledo XS3DU microbalance, Shimadzu IR-Prestige 21 infrared spectrophotometer (Shimadzu, Japan), Labline oven, Nuve deep freezer, desiccator, and an HPLC system (Shimadzu LC-20AD Prominence) equipped with an autosampler, diode array detector (Shimadzu, Japan), and a C18 Lichrospher® 100 endcapped column (250 × 4.0 mm i.d., 5 µm).

2.3. Sample Characterization

Characterization was conducted to confirm the identity of the tested samples using two methods: infrared spectrophotometry and high-performance liquid chromatography (HPLC).

2.3.1. Infrared Spectrophotometry Characterization

Glucosamine hydrochloride USPRS and glucosamine hydrochloride BPL were separately dispersed into 200 mg of potassium bromide, and absorption was measured using a Shimadzu IR-Prestige 21 spectrophotometer. Glucosamine hydrochloride USPRS and glucosamine hydrochloride BPL were separately dispersed into 200 mg of potassium bromide, and absorption was measured using a Shimadzu IR-Prestige 21 spectrophotometer.

2.3.2. High-Performance Liquid Chromatography (HPLC) Characterization

Standard and test solutions were prepared as follows. Standard solution: Glucosamine hydrochloride USPRS at a concentration of 1 mg/mL in the mobile phase. Test solution: Glucosamine hydrochloride BPL at a concentration of 1 mg/mL in the mobile phase.

Both test and standard solutions were injected into the HPLC system under the following conditions: C18 Lichrospher® 100 endcapped column (250 × 4.0 mm i.d., 5 µm); mobile phase consisting of 0.5 g sodium pentane sulfonate dissolved in 800 mL water, with 4 mL of 1M potassium hydroxide added, diluted to 1000 mL with water, followed by 430 µL perchloric acid and 50 mL acetonitrile. The flow rate was 0.5 mL/min, and detection was carried out at 195 nm using a diode array detector (DAD).

2.4. Method Validation and Stability Testing by HPLC

The validation parameters established included selectivity/specificity, accuracy, linearity, range, detection and quantification limits, and precision (repeatability and intermediate precision).

2.4.1. Selectivity/Specificity

Standard and test solutions (1 mg/mL each) were prepared as described in Section 2.3.2. The blank (mobile phase), standard, and test solutions were injected into the HPLC system under the same conditions.

2.4.2. Accuracy

The standard solution was prepared as described in the selectivity test. Two solutions of the same concentration were prepared and injected six times each into the HPLC system under the conditions described in the HPLC identification test. Accuracy was expressed as % bias.

The accuracy calculation is determined using the following formula:

$$Calculated\ content\ (\%) = \frac{r_2}{r_1} x \frac{C_1}{C_2} x\ Reference\ content\ (\%) \qquad \text{(Eq. 1)}$$

Accuracy is expressed as % bias, calculated using the following formula:

$$\%\ Accuracy\ (\%\ bias) = \left| \frac{Calculated\ content - Reference\ content}{Reference\ content} \right| x\ 100\% \qquad \text{(Eq. 2)}$$

Notes:

r_1	=	Mean peak response of standard solution 1
r_2	=	Mean peak response of standard solution 2
C_1	=	Concentration of standard solution 1 (%)
C_2	=	Concentration of standard solution 2 (%)
Reference content	=	Reference standard content on the label/certificate of analysis

2.4.3. Linearity and Range

Linearity solutions were prepared at five concentration levels: 0.50, 0.75, 1.0, 1.25, and 1.50 mg/mL. Each solution was injected and the area under the curve (AUC) was recorded. A calibration curve was plotted between concentration and AUC, and regression analysis was performed. Linearity was established based on the regression correlation coefficient (r).

2.4.4. Limit of Detection (LOD) and Limit of Quantification (LOQ)

LOD and LOQ were calculated statistically from the linear regression of the calibration curve in the linearity test.

$$LOD = \frac{3{,}3\ x\ SD}{slope\ (b)} \qquad \text{(Eq. 3)}$$

$$LOQ = \frac{10\ x\ SD}{slope\ (b)} \qquad \text{(Eq. 4)}$$

2.4.5. Precision

Standard and test solutions were prepared as described in the selectivity test. Solutions were injected into the HPLC system under identical conditions. Repeatability was assessed by injecting the test solution 10 times in a single day, while intermediate precision was

determined by conducting measurements on two different days. The relative standard deviation (RSD) of these measurements was calculated.

2.4.6. Short-Term Stability Testing

Ten vials of glucosamine hydrochloride BPL (200 mg each) were used. Samples were stored at –70°C (freezer) as a control, in duplicate. Short-term stability testing was performed at two different temperatures: 25°C and 60°C (three vials each). Samples were taken on days 3, 5, 7, and 10. After each sampling, vials were transferred to –70°C until further analysis. Stability testing was conducted using HPLC under the same conditions described in Section 2.3.2, with test solutions prepared at 1 mg/mL in duplicate.

2.4.7. Long-Term Stability Testing

Samples of glucosamine hydrochloride BPL were stored at 4–8°C and analyzed at 0 month (control), 72 months, and 144 months. Three vials were analyzed at each interval, in duplicate, using HPLC under the conditions described in Section 2.3.2.

2.4.8. Data Analysis

Stability test results were analyzed using the t-test. If t-count < t-table, the reference standard was considered stable. If t-count > t-table, the reference standard was considered unstable.
The stability evaluation is calculated using Equations (5–7) as follows:

$$t_{count} = \frac{b_i}{s_{bi}} \qquad \text{(Eq. 5)}$$

$$b_i = \frac{\sum_{i=1}^{n}(x_i-\bar{x})(y_i-\bar{y})}{\sum_{i=1}^{n}(x_i-\bar{x})^2} \qquad \text{(Eq. 6)}$$

$$s_{bi} = \frac{s}{\sqrt{\sum_{i=1}^{n}(x_i-\bar{x})^2}} \qquad \text{(Eq. 7)}$$

Notes:
x_i = time (months for LTS, hours for STS)
y_i = concentration (%)

3. Results and Discussion

3.1. Infrared Spectrophotometry Characterization

The infrared absorption spectrum of glucosamine hydrochloride showed characteristic absorption bands at 1617, 1584, 1539, 1420, 1249, 1094, 1033, and 912 cm^{-1}. The infrared spectrophotometric identification produced identical profiles and fingerprint spectra between glucosamine hydrochloride BPL and glucosamine hydrochloride USPRS, as presented in Figure 2.

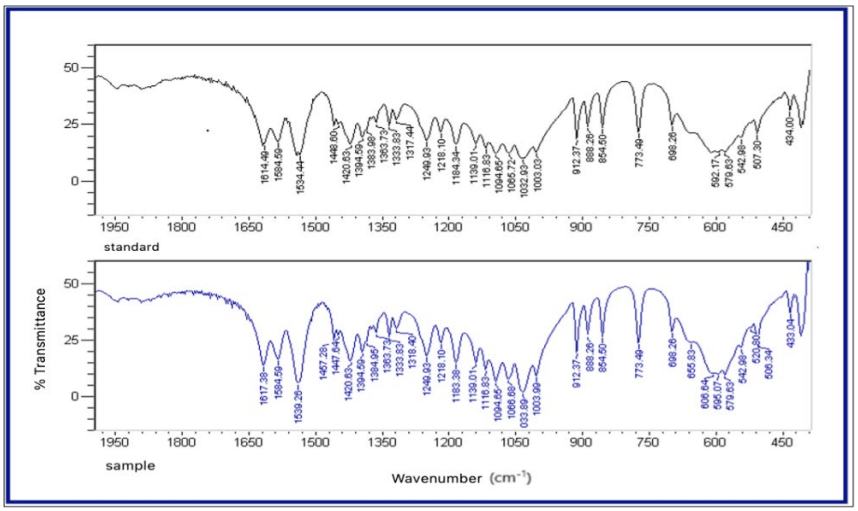

Figure 2. Infrared spectra of glucosamine hydrochloride USPRS (top) and glucosamine hydrochloride BPL (bottom)

The O–H stretching frequency overlapped with the C–H stretching frequency. Wavenumbers at 1384 cm^{-1} and 912 cm^{-1} indicated the presence of C–H bonds; wavenumbers between 1500–1700 cm^{-1} showed the presence of an amine group; wavenumbers at 1318–1249 cm^{-1}, 1183 cm^{-1}, and 1139 cm^{-1} indicated the presence of C–OH bonds. The wavenumber at 1617 cm^{-1} corresponded to C–C stretching vibrations and N–H bending. The wavenumber at 1094 cm^{-1} indicated the presence of secondary alcohol –OH. Peaks at 854 cm^{-1} and 773 cm^{-1} were due to meta-substituted ring groups. Based on these results, the compound was confirmed to be glucosamine hydrochloride.

3.2. High-Performance Liquid Chromatography (HPLC) Characterization

HPLC-DAD characterization aimed to determine analyte retention time and peak spectrum. The results (Figure 3) showed that the retention time of the major peak in the glucosamine hydrochloride test solution chromatogram matched the main peak in the standard solution chromatogram at 3.33 minutes, confirming the identity of the test sample as glucosamine hydrochloride.

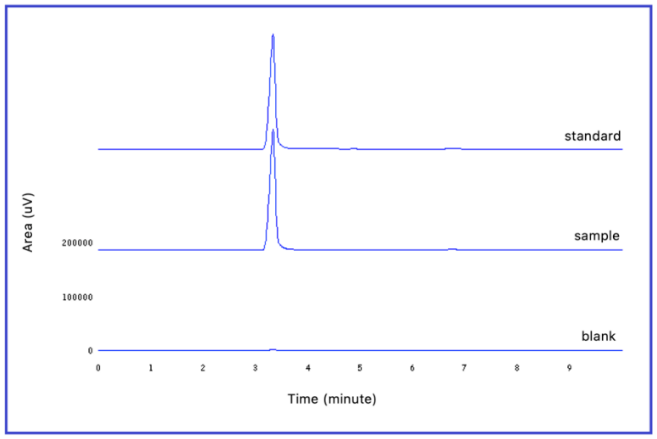

Figure 3. HPLC chromatogram of glucosamine hydrochloride (C18 Lichrospher® 100 endcapped, 250 × 4.0 mm i.d., 5 µm; mobile phase: 0.5 g sodium pentane sulfonate dissolved in 800 mL water + 4 mL 1M potassium

hydroxide, diluted to 1000 mL with water, 430 µL perchloric acid, and 50 mL acetonitrile; flow rate: 0.5 mL/min; detection: 195 nm with DAD).

3.3. Method Validation

System suitability testing included chromatographic parameters such as tailing factor, theoretical plates, and injection repeatability. The glucosamine hydrochloride peak had a tailing factor of 0.96 with 3,621.25 theoretical plates. Injection repeatability yielded relative standard deviations (RSD) of 0.18% for peak area and 0.07% for retention time. These results confirmed that the HPLC system met analytical validation requirements and demonstrated good precision.

Table 1. System suitability test for glucosamine hydrochloride

Parameter	Result	Criteria (USP, 2020)
Tailing factor	0,96	≤ 1,5
Theoretical plates	3621,25	≥ 2000
RSD area (%)	0,18	≤ 2,0 %
RSD retention time (%)	0,07	≤ 1,0 %

The blank chromatogram showed no peaks with retention times identical to the major peak in the standard chromatogram (Figure 3). The main peak in the test chromatogram matched the main peak in the standard chromatogram. Thus, the method was confirmed to be selective and specific for glucosamine hydrochloride analysis by HPLC.

Accuracy was determined by calculating the % bias between measured concentrations and the certified concentration stated in the CoA (certificate of analysis). The mean accuracy obtained was 0.43%, meeting the acceptance criterion of % bias ≤ 2.0% (Ahuja, 2005). This demonstrated that the method was accurate and valid for quantifying the glucosamine hydrochloride BPL reference standard.

Linearity was assessed using calibration curves for glucosamine hydrochloride (Figure 4). The curve was linear across 0.48–1.45 mg/mL, with the regression equation $y = 1{,}575{,}103.591x + 87{,}841.200$ and correlation coefficient (R) of 1.000, satisfying the requirement of $R \geq 0.995$ (AOAC, 2002). The limit of detection (LOD) and limit of quantification (LOQ) were 0.014 µg/mL and 0.047 µg/mL, respectively.

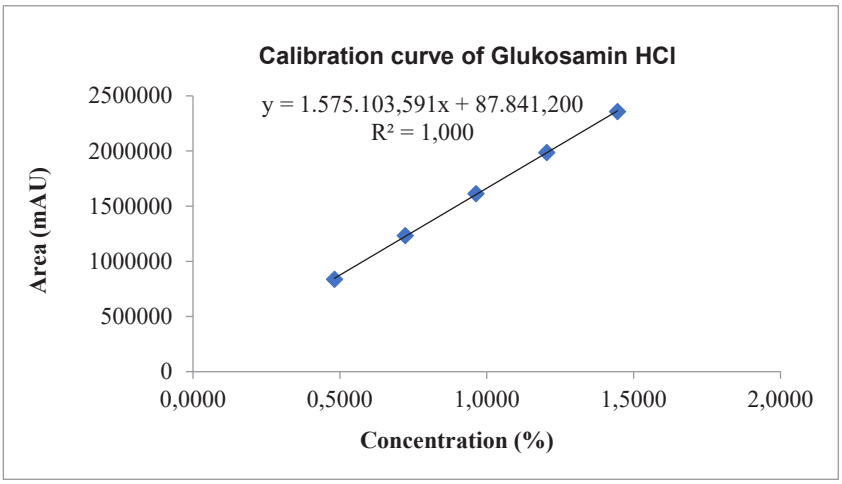

Figure 4. Calibration curve of glucosamine hydrochloride

Precision is a measure that indicates the degree of agreement among individual test results, assessed through the distribution of individual values around the mean when the procedure is applied to replicate samples taken from a homogeneous mixture. Precision can yield repeatability values that are close together, with standard deviation (SD) or relative standard deviation (RSD) used as parameters (ICH, 2005). The precision parameters evaluated in this study included system precision, method precision, and intermediate precision conducted on two different days. System precision, obtained from repeated injections of the standard solution, showed RSD values of less than 2.0%. Method precision on two different days in this study was 0.60% and 0.36%, while intermediate precision was 0.48%. An RSD value of less than 2% indicates that the precision parameters provided acceptable repeatability.

3.4. Stability Testing

This study conducted both short-term and long-term stability testing of glucosamine hydrochloride BPL to ensure its stability during transport, distribution, and storage.

Short-Term Stability at 25°C and 60°C, samples were tested over 0, 72, 120, 168, and 240 hours (Figures 5 and 6). Both curves showed slopes close to zero. Statistical analysis using the t-test showed t-count < t-table. At 25°C, t-count = –2.738 < 2.306, and at 60°C, t-count = 0.976 < 2.306. These results confirmed that glucosamine hydrochloride BPL remained stable for up to 10 days under these conditions, indicating its quality was preserved during short-term transport and distribution at 25°C and 60°C.

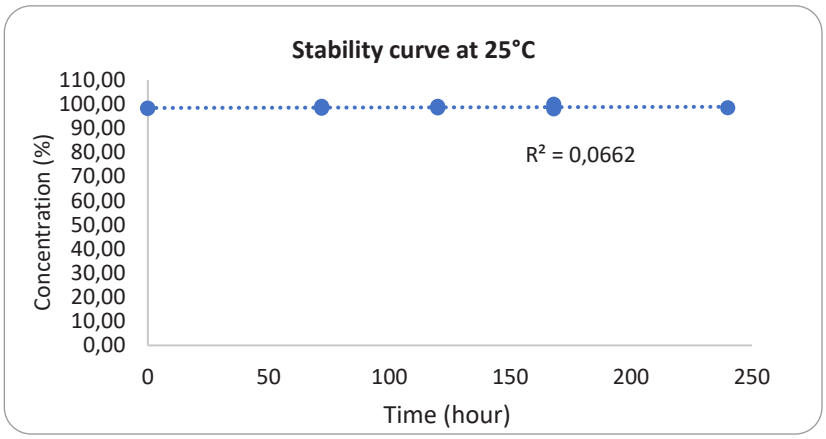

Figure 5. Short-term stability curve of glucosamine hydrochloride at 25°C

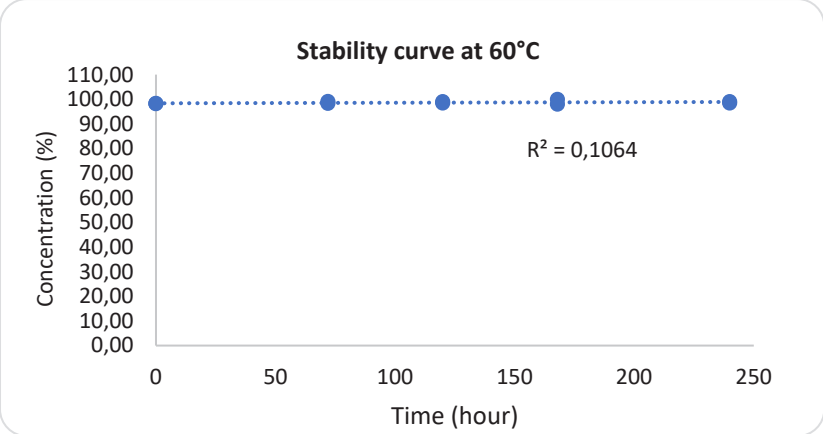

Figure 6. Short-term stability curve of glucosamine hydrochloride at 60°C

Long-term stability testing, also serving as quality monitoring of the produced reference standard, demonstrated that glucosamine hydrochloride BPL was stable at the recommended storage temperature (4–8°C) for up to 144 months. The slope of the curve was close to zero (Figure 7), and statistical analysis showed t-count = –8.793 < 2.032, meeting stability criteria. This proved that glucosamine hydrochloride BPL is stable under recommended storage and distribution conditions, ensuring product reliability in the pharmaceutical industry.

Based on its physicochemical properties, glucosamine hydrochloride is relatively stable at room temperature. However, prolonged exposure to high temperatures can cause degradation, potentially damaging its glucosamine ring or cleaving the hydrochloride component, leading to impurities. Decomposition may occur above 150°C. Furthermore, glucosamine hydrochloride is hygroscopic, absorbing moisture from the environment, which can accelerate degradation, form unwanted byproducts, and shorten shelf life. It must therefore be stored in tightly sealed, moisture-resistant containers under dry conditions. It is stable when kept away from direct sunlight, as prolonged light exposure, particularly UV radiation, can cause degradation, discoloration, and reduced effectiveness. Thus, storage in light-resistant containers is essential (Kompantsev, 2012; Pan et al., 2023).

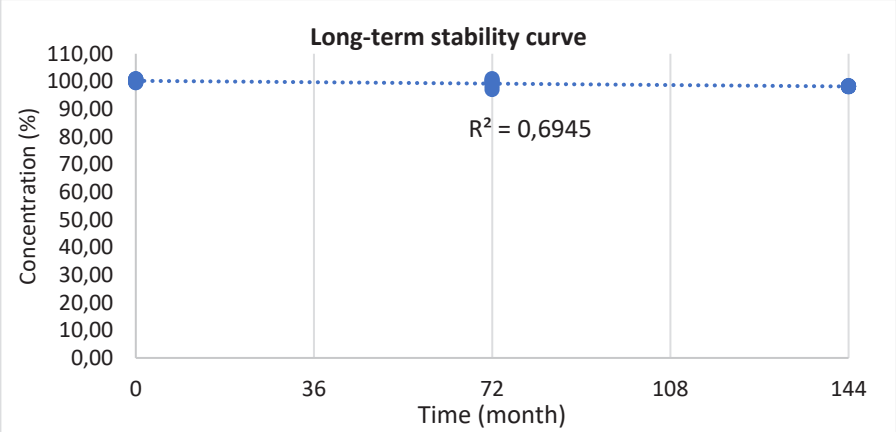

Figure 7. Long-term stability curve of glucosamine hydrochloride at storage temperature

Over time, glucosamine hydrochloride may form impurities due to environmental factors or improper storage. These include hydrolysis and thermal degradation byproducts, which can compromise its quality. Therefore, the reference standard should be stored in tightly closed containers, in cool, dry places, protected from light and excessive heat (Chauhan & Choudhari, 2018).

When compared with Glucosamine hydrochloride USPRS, which has an expiry period of 72–84 months (United State Pharmacopoeia, 2024), glucosamine hydrochloride BPL produced by PPPOMN demonstrated twice the stability. This highlights the superior quality of glucosamine hydrochloride BPL, making it a reliable reference standard for pharmaceutical testing.

4. Conclusion

Glucosamine hydrochloride BPL was shown to be stable at the recommended storage temperature of 4–8°C for up to 144 months (12 years) and under transport or distribution conditions at 25°C and 60°C for up to 10 days. However, further studies with longer storage durations at 25°C and 60°C are necessary to confirm extended stability under these conditions. Overall, glucosamine hydrochloride BPL demonstrated assured quality and can be used as long as it is stored under the recommended storage conditions and shelf life. Information regarding storage conditions and shelf life should be clearly stated on the reference standard label.

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