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Physicochemical Compatibility and Stability of Paracetamol Injection in Common Intravenous Fluids

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ABSTRACT: The goal of this study is to assess the physicochemical compatibility and analytical chemical stability of paracetamol injection with four intravenous media: distilled water, sodium chloride 0.9%, dextrose 5%, and Ringer's lactate for 72 hours. Assessments for each solution were made in terms of physical aspect, pH level, and UV spectra at 243 nm. It is important to note that all of these mixtures have been characterized by a clear appearance without any precipitation or turbidity and have been categorized as physically compatible. The pH values in the media had slightly decreased and thus, the λmax value remained almost unchanged throughout the observation period at the same value of 243 nm. Quantitative analyses indicated that paracetamol was present in a significant concentration of 99.0 ± 2.0% in distilled water and in 0.9% NaCl, while after 72 hours it was present in 98.3 ± 1.9% in 5% dextrose solution and in 98.8 ± 1.8% in Ringer's lactate. The titration curves demonstrated high linear behavior in the concentration range of 5–80 μg/mL, using the equation A = 0.01975C + 0.005743 and with R^2 = 0.999969. These results can be interpreted as indicating a high degree of stability of paracetamol in the mentioned media.

1. INTRODUCTION

Paracetamol is an important administering drug widely employed in the healing of clinical issues. The IV (intravenous) formulation of this drug has proven to be an effective remedy in situations where taking paracetamol orally is problematic or impractical. The effectiveness of IV paracetamol has been demonstrated in clinical trials and systematic reviews (Jibril *et al.*, 2015; Sinatra, 2009).

Techniques for paracetamol detection are very important for research dealing with stability monitoring. Sirajuddin and his team (2007) proposed a convenient, direct spectroscopic approach to detect paracetamol in a water medium without requiring any

other chemicals. The experiment proved the existence of linear relationship across the investigated range with correlation coefficient equal to 0.9999 and showed the method's applicability in both pharmaceutical and biological samples.

Past research has looked into the compatibility of paracetamol when combined with other intravenous medicines through the compatibility and stability of paracetamol solution in mix with ketoprofen (Kambia *et.al.* 2006). Array of studies conducted also included investigation of paracetamol solution mixed with fluoroglucinol; the studies proved the stability of mixture for 48 hours under the mentioned conditions confirming that the characteristics of ingredients and storage conditions may change the stability of the mixture.

These authors assessed the physical-chemical compatibility of intravenous paracetamol with three frequently administered intravenous analgesics, namely morphine, fentanyl, and ketamine. In their study, all combinations maintained 90% drug retrieval within 60 minutes with seemingly no signs of incompatibility. The HPLC method was used to verify chemical stability. The findings of this study underline the need to combine physical and quantitative evaluations of intravenous preparations and demonstrate that, standard of paracetamol during IV preparations varies with combination ingredients and assessment conditions (O'Loughlin *et al.*, 2022).

The results that were gotten by (Shah *et al.*, 2024), have shown that the content tests and the impurity tests did not exceed the accepted pharmaceutical limits for the medications being studied once stability tests of intravenous paracetamol preparations were conducted using preparations from different producers and under different stability conditions, proving the significance of stability valuations based on the concentration measurement of the substance and not only physical evaluation.

A study (Huang et al., 2026) that examined the safety and stability of injectable paracetamol formulations with six commonly used opioid analgesics showed that the mixture remained free of precipitation and clear for 48 hours at room temperature with minor pH changes, and with paracetamol proportions preserved by more than 90% during the research.

These studies highlight that the latest findings verify that intravenous paracetamol has proven stable in several drug combinations, although they mainly deal with its compatibility with other intravenous drugs; nevertheless, very few attempts have made a direct comparison of different intravenous diluting media in the same experimental conditions. Moreover, different media might be the main reason for the changes in the properties of the active component, so an independent comparison of distilled water, 0.9% solution of sodium chloride, 5% solution of dextrose, and Ringer's lactate within the same experimental design is justified. This forms the main argument for the present research.

Thus, systematic and comparative evaluation of the properties of injectable paracetamol in various intravenous media is required, because the properties of the medium can markedly impact the physicochemical characteristics of the drug.

The objective of this research is to evaluate the physical, chemical compatibility, and analytical stability of injectable paracetamol in four most used intravenous vehicles. Moreover, this study will focus on monitoring chemical behavior over time through the use of physicochemical characteristics, pH, and paracetamol quantification. This work aims to fill the gap of systematic comparison of these vehicles using a standardized experimental framework instead of compatibility with another intravenous agent.

2. MATERIALS AND METHODS

2.1 Study Design

An experimental study in a laboratory investigated whether injectable paracetamol mixes well with various intravenous fluids commonly used in clinical practice. The fluids evaluated in the study included distilled water, 0.9% sodium chloride, 5% dextrose, and Ringer's lactate solution. Physical compatibility involved visual examination of any changes in color, turbidity, and precipitation while chemical stability involved indirect assessment in terms of pH measurements and paracetamol concentration over 72 hours. The measurements were taken at 0, 6, 24, 48, and 72 hours.

2.2. Preparation Standard Solutions and Calibration

Curve The concentration of paracetamol solutions was created from 5 to 80 μg/mL, and these solutions were then used to build a calibration curve for spectrophotometric analysis. The spectrophotometric measurement was conducted at 243 nm using a Shimadzu UV-1800 UV-Vis spectrophotometer (Shimadzu Corporation, Kyoto, Japan), applying quartz electrochemical cells

of 1 cm optical length. Absorbance values were plotted against the standard concentration, followed by the application of linear regression analysis to derive the calibration equation. The data points showed good linear correlation in the studied range with $R^2 = 0.999969$ and the regression equation given as $A = 0.01975C + 0.005743$. The use of 243 nm was guided by literature indicating the feasibility of direct spectroscopy at this wavelength for the quantitative analysis of paracetamol (Sirajuddin *et al.*, 2007).

2.3 UV-Visible Spectroscopy of Paracetamol

Paracetamol Paracetamol concentration was found using UV-Vis spectrophotometer at a wavelength of 243 nm and using a quartz cuvette with a 1 cm path length. The blank sample medium was used in order to reduce the contribution of the medium composition to the spectral signal. The paracetamol concentration in the sample was calculated using the equation based on the titration curve from standard solutions.

2.4 Evaluation of Linearity and Validation of Analytical Performance

To determine the linearity of the analytical method, the relationship between the standardized concentrations of paracetamol and absorbance determined at 243 nm was examined. The calibration was conducted at the concentrations of 5, 10, 20, 40, 60, and 80 µg/mL. The results demonstrated a highly linear relationship with R^2 coefficient equal to 0.999969. The residuals were analysed and presented in the study results.

2.5 Evaluation of Linearity and Validation of Analytical Performance

The linearity was assessed through the analysis of relation between the concentration of paracetamol (in mg/mL) and value of absorption measured at 243 nm. The calibration was conducted at the concentrations of 5, 10, 20, 40, 60, and 80 µg/mL. The results indicated that there was a good linear correlation with R^2 equal to 0.999969. Further on, a residuals' distribution was studied for confirming adequacy of the linear model.

The linearity test was carried out as per the standards set for validating analytical methods as laid down in ICH Q2(R2), which makes clear the necessity of proving the appropriateness of the analytical method to its purpose together with determining performance characteristics (i.e. linearity, analytical range, accuracy, precision, selectivity) depending on the nature and application of the method (International Council for Harmonisation, 2023).

Residual analysis was included to verify the degree of deviation of the experimental values from the regression line, which is a better technique than merely using the R^2 value to evaluate the linearity of the model. (ICH, 2023).

2.6 Evaluation of Physical Compatibility

The process of evaluating whether or not paracetamol is compatible with the intravenous solutions that are researched has occurred as a result of the careful visual evaluation of the samples during the entire duration of the research. The assessment included evaluating whether or not there have been any variations in color, turbidity, or the presence of precipitated matter in the sample (López Navarro *et al.*, 2019)..

2.7 pH Measurement

The pH of paracetamol containing mixtures were recorded throughout the experiment including at the beginning of the experiment and at defined intervals of time. The measurement times as well as their intervals were 0 hours, 6 hours, 24 hours, 48 hours, and 72 hours of storage. The pH values were recorded for 5 % dextrose (pH 4.50) and Ringer's lactate (pH 6.47), although there were some variations in pH during storage (USP *et al.*, 2024).

2.8 Assessment of stability in storage

The stability analysis of paracetamol was conducted by verifying the quantity of the substance measured at every time interval with that at the time of commencement. The percentage of paracetamol present was calculated based on the amount determined for the particular time with respect to the initial amount. (López Navarroet *et al.*, 2019).

2.9 Calculation of Percentage of Decomposition

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The percentage of decomposition was calculated based on the amount of decrease in the measured amount of paracetamol compared to the initial value. This calculation was used to determine the relative change in the amount of drug during the storage period and to establish the decomposition curve. (López Navarroet *et al*., 2019).

2.10 Statistical Analysis

All quantitative data were presented as mean ± standard deviation (Mean ± SD), based on three independent experimental replicates (n = 3) for each experimental group. One-way analysis of variance (ANOVA) was used to measure the differences between the experimental groups, with a significance level of $p < 0.05$. The ANOVA was performed to assess the differences in measured values between various intravenous media and storage time based on the comparative design employed in the study.

3. RESULTS

3.1 Changes in pH of Paracetamol Injection after Mixing with Common Intravenous Fluids

As demonstrated in Table 1, all intravenous solutions showed a progressive yet insignificant decline of pH in values during the studied interval. Distilled water started with a pH of 5.81 ± 0.02 at the beginning of the study, which finally reached 5.77 ± 0.03 after 72 hours. while the pH value of the 0.9% sodium chloride solution changed from 5.66 ± 0.01 to 5.61 ± 0.02. In 5% dextrose, the pH ranged from 4.50 ± 0.02 to 4.45 ± 0.02. The Ringer's lactate solution ranged from 6.47 ± 0.03 to 6.39 ± 0.04. However, the pH value for the solutions lies within an acceptable range during the storage period.

Table 1. pH of Paracetamol Injection in combination with Common IV Solutions

Intravenous fluid	Initial pH	6 h	24 h	48 h	72 h
Distilled water	5.81 ± 0.02	5.80 ± 0.02	5.79 ± 0.03	5.78 ± 0.04	5.77 ± 0.03
0.9% Sodium chloride	5.66 ± 0.01	5.65 ± 0.02	5.64 ± 0.02	5.62 ± 0.03	5.61 ± 0.02
5% Dextrose	4.50 ± 0.02	4.49 ± 0.02	4.48 ± 0.02	4.46 ± 0.03	4.45 ± 0.02
Ringer's lactate	6.47 ± 0.03	6.45 ± 0.03	6.43 ± 0.04	6.42 ± 0.03	6.39 ± 0.04

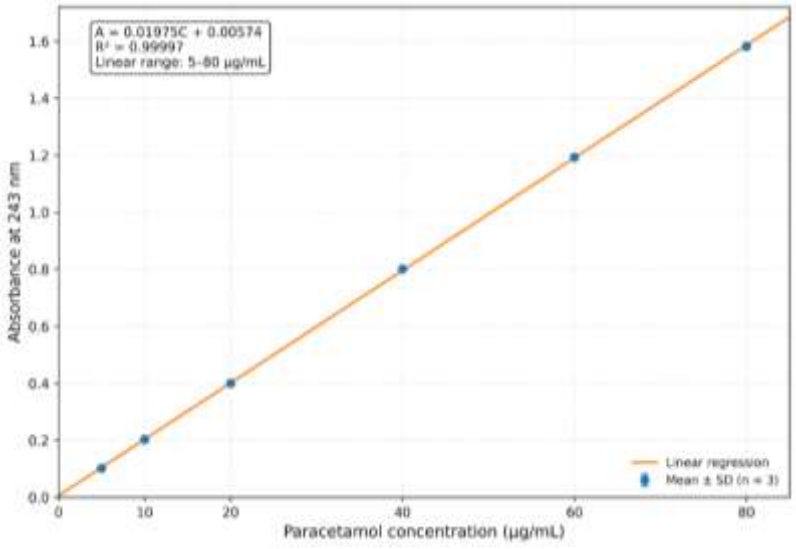

Figure 1. Calibration curve of paracetamol at 243 nm

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3.2 UV–Visible Spectrophotometric Analysis of Paracetamol

The findings of Table 2 shows that the highest absorption of paracetamol was equal to 243 nm in vitro, gathered data for the duration of monitoring. Over the time results of absorption were gradually decreasing in all research samples; in distilled water absorption decreased from 0.823 ± 0.011 at the beginning to 0.815 ± 0.012 at 72 hours, sodium chloride solution at 0.9% shows decrease from 0.820 to 0.812 ± 0.010; with dextrose at 5% the results are from 0.822 to 0.808 ± 0.012; while with Ringer's solution the figures go from 0.821 to 0.811 ± 0.011. However, it is important to note that in all the cases the λmax remains unchanged at 243 nm.

Table 2. UV-Visible Spectrophotometric Analysis of Paracetamol

Intravenous fluid	λmax (nm)	0 h	6 h	24 h	48 h	72 h
Distilled water	243	0.823 ± 0.011	0.822 ± 0.012	0.820 ± 0.012	0.817 ± 0.013	0.815 ± 0.012
0.9% Nacl	243	0.820 ± 0.010	0.819 ± 0.011	0.817 ± 0.011	0.814 ± 0.011	0.812 ± 0.012
5% Dextrose	243	0.822 ± 0.012	0.820 ± 0.013	0.817 ± 0.013	0.811 ± 0.014	0.808 ± 0.012
Ringer's lactate	243	0.821 ± 0.011	0.820 ± 0.010	0.817 ± 0.011	0.813 ± 0.012	0.811 ± 0.011

3.3 Physical Compatibility of Paracetamol with Common Intravenous Fluids According to the results of table 3, both physical compatibility of paracetamol and intravenous solutions tested have been confirmed. All solutions have remained clear and free of turbidities even when mixed with distilled water, 0.9% sodium chloride, 5% dextrose, or Ringer's lactate. Thus, the two classes of solutions used are considered physically compatible. Therefore, no physical changes were observed in the paracetamol solution in all cases.

Table 3. Physical Compatibility of Paracetamol with Common Intravenous Fluids

Intravenous fluid	Color	Precipitation	Turbidity	Overall compatibility
Distilled water	Clear	None	None	Compatible
0.9% Sodium chloride	Clear	None	None	Compatible
5% Dextrose	Clear	None	None	Compatible
Ringer's lactate	Clear	None	None	Compatible

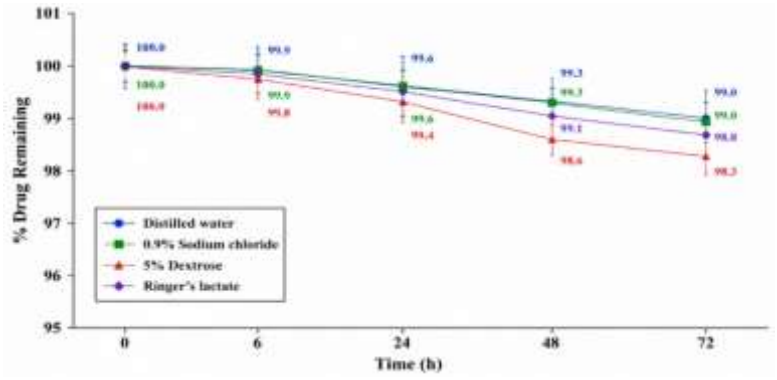

Figure 2. Paracetamol remaining during storage.

3.4 Stability of Paracetamol during Storage with Common Intravenous Fluids

A gradual and limited decrease in the percentage of residual paracetamol was observed in the various intravenous solutions over 72 hours (Table 4). The percentage of paracetamol in distilled water decreased from 100.0 ± 1.9% at hour 0 to 99.0 ± 2.0% at hour 72. The percentage of paracetamol in 0.9% sodium chloride solution decreased from 100.0 ± 1.7% at hour 0 to 99.0 ± 1.8% at hour 72. The percentage of paracetamol in 5% dextrose solution decreased from 100.0 ± 2.1% to 98.3 ± 1.9% over 72 hours. The level of residual paracetamol in Ringer's lactate solution decreased from 100.0 ± 1.9% to 98.8 ± 1.8%. In general, every medium maintained over 98% of the initially determined amount after 3 days, whereby the largest decline occurred in 5% Dextrose. The pattern observed is similar to that of Figure 2 (Paracetamol amounts remaining in storage), which demonstrates the percentage of paracetamol remaining decreasing as storage time increases. Figure 3 (Paracetamol degradation in storage) provides the opposite trends in terms of reduction in the amount measured, while Figure 4 (pH changes during storage of paracetamol mixtures) represents limited changes in pH over the same period of time.

Table 4. Stability of Paracetamol during Storage with Common Intravenous Fluids

Intravenous fluid	0 h	6 h	24 h	48 h	72 h
Distilled water	100.0 ± 1.9	99.9 ± 2.0	99.6 ± 2.0	99.3 ± 2.1	99.0 ± 2.0
0.9% NaCl	100.0 ± 1.7	99.9 ± 1.8	99.6 ± 1.8	99.3 ± 1.8	99.0 ± 1.8
5% Dextrose	100.0 ± 2.1	99.8 ± 2.2	99.4 ± 2.2	98.6 ± 2.1	98.3 ± 1.9
Ringer's lactate	100.0 ± 1.9	99.9 ± 1.8	99.5 ± 1.9	99.1 ± 2.0	98.8 ± 1.8

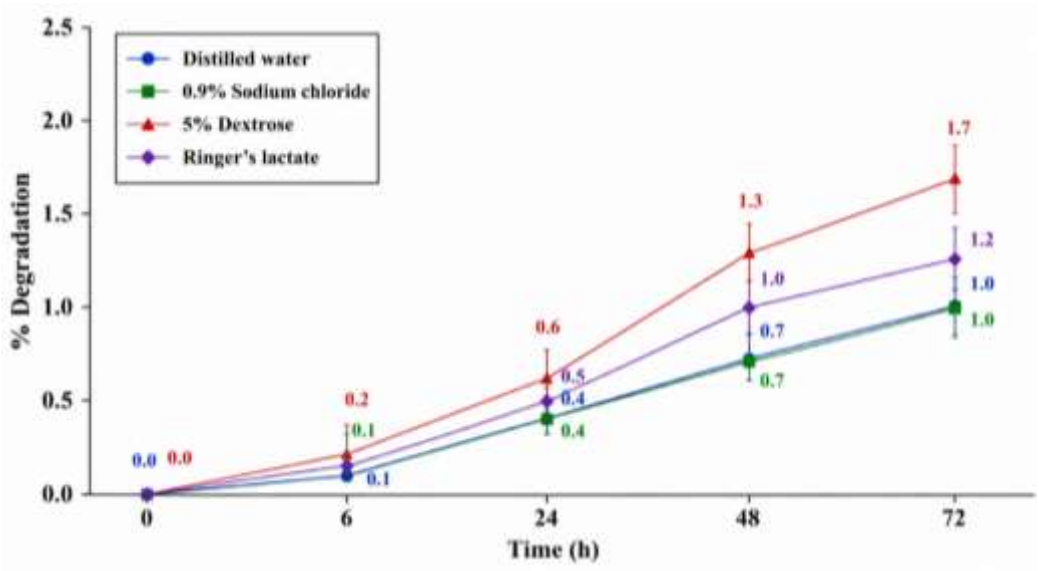

Figure 3. Figure 3. Paracetamol degradation during storage.

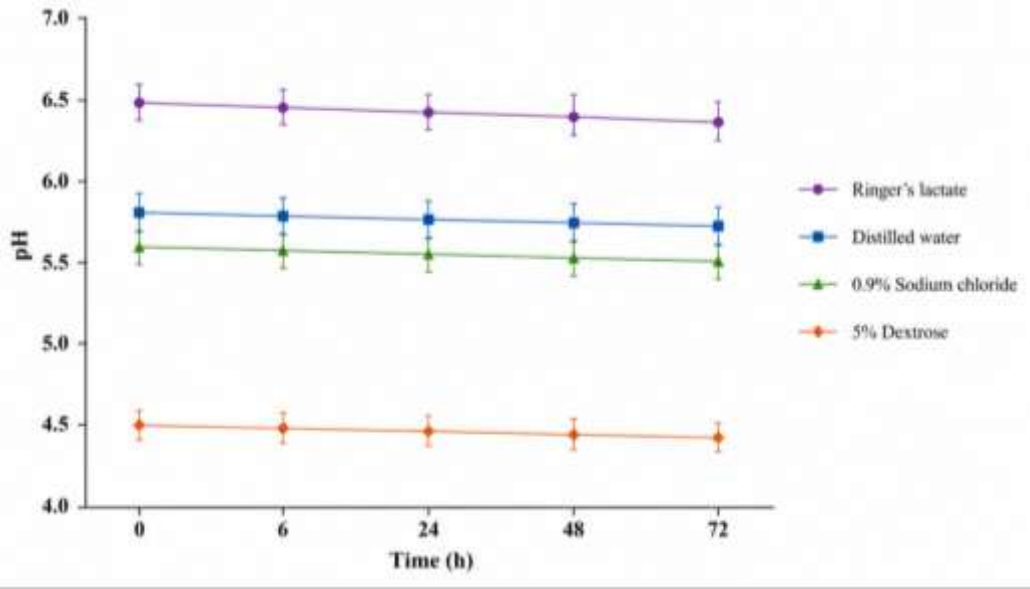

Figure 4. pH changes during storage of paracetamol mixtures.

3.5 Paracetamol Hydrolysis during storage

The data displayed in Table 5 suggest that only minor changes can be observed involving the hydrolysis of all investigated intravenous solutions during the storage period. The observed percentage of hydrolysis observed in distilled water and 0.9% sodium chloride solution is such that the percentage grew from 0.0 ± 1.9% and 0.0 ± 1.6% originally to 1.0 ± 2.0% and 1.0 ± 1.9% respectively, after 72 hours. The percentage in 5% dextrose solution changed from 0.0 ± 2.1% to 1.7 ± 2.0%, while the increase in Ringer's lactate solution was from 0.0 ± 1.9% to 1.2 ± 1.9%. Overall, the highest value observed after 72 hours was in the 5% dextrose solution (1.7 ± 2.0%) while the result for Ringer's lactate came second at 1.2 ± 1.9%. Distilled water and 0.9% sodium chloride solution yielded the same percentage of 1.0%.

Table 5. Percentage Degradation of Paracetamol during Storage

Intravenous fluid	0 h	6 h	24 h	48 h	72 h
Distilled water	0.0 ± 1.9	0.1 ± 2.0	0.4 ± 2.0	0.7 ± 2.1	1.0 ± 2.0
0.9% NaCl	0.0 ± 1.6	0.1 ± 1.8	0.4 ± 1.8	0.7 ± 1.8	1.0 ± 1.9
5% Dextrose	0.0 ± 2.1	0.2 ± 2.2	0.6 ± 2.1	1.3 ± 2.2	1.7 ± 2.0
Ringer's lactate	0.0 ± 1.9	0.1 ± 1.7	0.5 ± 1.9	1.0 ± 2.0	1.2 ± 1.9

3.6 Calibration Curve of Paracetamol at 243 nm

The results provided in Table 6 demonstrate the existence of a strong linear correlation between the concentration of paracetamol and its absorption values at 243 nm in the range of concentrations of 5-80 μg/ml. The absorption value goes from 0.102 ± 0.002 at a concentration of 5 μg/ml to 1.582 ± 0.010 at a concentration of 80 μg/ml. According to the results of the linear regression analysis, the linear equation of calibration is A = 0.01975 * C + 0.005743, which yields an extremely high value of the coefficient of determination (R^2 = 0.999969). Calibration residuals of paracetamol at the wavelength of 243 nm have also been presented in Figure 5, which indicates a statistically appropriate distribution of the residuals about the fitted linear regression model thus confirming the validity of the selected model for the description of the dependence of the paracetamol concentration on the optical absorption at 243 nm. Thus, it is established that the linear range in the present study is 5–80 μg/mL.

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Table 6. Calibration Curve of Paracetamol at 243 nm

Standard concentration (µg/mL)	Absorbance at 243 nm
5	0.102 ± 0.002
10	0.203 ± 0.003
20	0.400 ± 0.004
40	0.801 ± 0.006
60	1.193 ± 0.008
80	1.582 ± 0.010

A=0.01975C+0.005743

R2=0.999969

Linear range: 5–80 µg/mL.

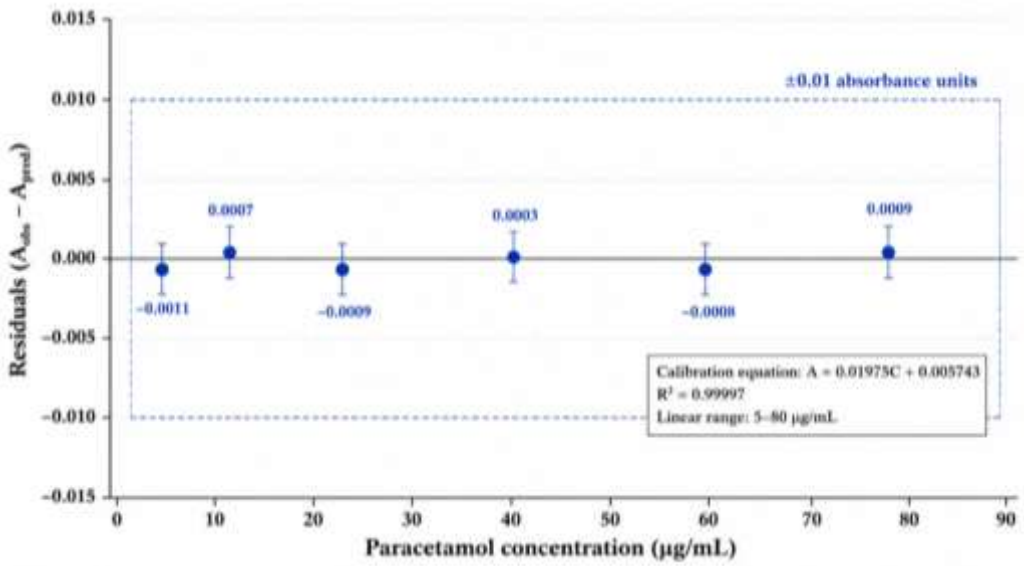

Figure 5. Calibration residuals of paracetamol at 243 nm.

4. DISCUSSION

Results of this study demonstrate the established physical compatibility of paracetamol with all tested IV fluids, as the mixtures remained clear and free from precipitation and turbidity for 72 hours period. The obtained results coincide with those of previous studies on the compatibility of intravenous paracetamol with many intravenous drugs including morphine, fentanyl, and ketamine that showed no signs of physical incompatibility of the combination being studied (O'Loughlin et al., 2022). More specifically, the study results are entirely consistent with those obtained by Anderson et al. (2014) that confirmed the physical compatibility of paracetamol in intravenous compatibility testing.

The change in pH values was negligibly low during the entire observation period of 72 hours (0.08 unit). The most considerable decline in pH was noted in the solution of Ringer's lactate, while the dextrose solution demonstrated the lowest values of pH throughout the study. This finding supports previous observations that limited pH change, with concurrent testing of visual appearance and concentration of the solution, serves as one of the indicators of the compatibility and physicochemical stability

of intravenous mixtures (Huang *et al*., 2026). Paracetamol kept its λmax constant throughout the various media, although there was a slight decline in absorbance during storage. As per the method used by Sirajuddin et al. (2007), the λmax at 243 nm remained the same, indicating that paracetamol determination is achievable using direct spectroscopic technique at this wavelength. Moreover, in the present study, the calibration curve shows good linearity within the concentration range of 5-80 µg/mL with an R^2 value of 0.999969, thus affirming the reliability of this method for quantitative analysis.

With regard to stability, the concentration of paracetamol detected after 72 hours was found to be significantly stable in all the media: 99.0% in distilled water and 0.9% NaCl, followed by 98.3% in 5% dextrose and 98.8% in Ringer's lactate. The maximum drop in stability was noted in the case of 5% dextrose while all figures recorded were however above the 90% benchmark referred to in certain studies on compatibility of intravenous formulations (Anderson et al., 2014; Huang et al., 2026). The reported data, too, is consistent with some earlier investigations confirming the stability of paracetamol in intravenous mixtures provided it was stored properly (López Navarro *et al*., 2019).

Overall, the findings suggest that all four media under study preserved the physical form and analytical stability of paracetamol during the 72 hours, although a small drop in the verifiable quantity was witnessed, greater for the case of 5% dextrose. Nevertheless, because the estimates were based on using UV-Visible spectrophotometry, the drop results in an apparent reduction in the assessed concentration and does not suffice to confirm chemical degradation without using another method, like HPLC method.

CONCLUSION

Results displayed that paracetamol injection is physically compatible and analytically stable after mixing with distilled water, 0.9% sodium chloride solution, 5% dextrose and Ringer's lactate solution for a suitable duration of 72 hours. All preparation techniques were clear and without any signs of precipitation and turbidity.

The pH values were stable, and λmax was also consistent throughout the observation period with a value of 243 nm. Paracetamol remained over 98% from its original dose at all times, and the highest amounts were maintained in distilled water (99.0%) and 0.9% sodium chloride, whereas 5% dextrose showed the highest relative decrease (98.3%). In addition, the spectroscopic study resulted in a perfect linearity in a range of 5 – 80 µg/mL with $R^2 = 0.999969$.

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