# Compatibility test of intravenous preparations of phenytoin

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**Compatibility test of intravenous preparations of phenytoin**

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## ABSTRACT

The reconstitution of intravenous phenytoin in normal saline was observed to decrease the stability of the preparation. This study aims to assess the physical and chemical incompatibilities of IV phenytoin in normal saline over a specified timeframe. The research was conducted in two phases. In the first phase, physical testing of IV phenytoin in normal saline included assessments of organoleptic properties, particle size, and pH, with measurements taken at 0, 3, and 6 hours. In the second phase, chemical stability was evaluated by measuring the concentration of the preparation over an 8-hour period, as well as analyzing the functional groups of IV phenytoin precipitates in normal saline via FTIR and GC-MS. The results of the concentration tests for phenytoin samples A, B, and C indicated instability. IR testing of the precipitates revealed the presence of specific functional groups: the amide C=O group at 1752 $cm^{-1}$, the phenyl C-H group at 744 $cm^{-1}$, the amide N-H group at 1639 $cm^{-1}$, the C-N group at 1286 $cm^{-1}$, and the phenyl C=C group at 1504 $cm^{-1}$. Physical testing showed no pH increase exceeding 1 unit across samples at 0, 3, and 6 hours, although there was an observable increase in turbidity, consistent with organoleptic particle size analysis. Molecular weight testing between pure phenytoin and the precipitated sample revealed identical values of 180.1 m/z. Variations in physical compatibility among the three sample sources may be attributable to differences in excipients used in their respective formulations.

**Keywords**: phenytoin, dosage concentration, functional groups, particle size, pH

## INTRODUCTION

Intravenous (IV) preparations commonly administered in hospitals include [i1]phenytoin (1,2), a medication used in seizure therapy (3). IV phenytoin is typically reconstituted in normal saline (4).; however, it becomes unstable over time (5,6). leading to potential chemical and physical incompatibilities (7).These instabilities merit close attention, as they can impact therapeutic effectiveness.

Proper reconstitution of IV phenytoin requires monitoring parameters such as pH, turbidity, and particle size. Phenytoin solutions generally have a pH of 10–12 (4) , while normal saline ranges from pH 5 to 7. This significant pH discrepancy can promote precipitation 0). Mixing IV phenytoin with KA-EN 1B has been shown to increase turbidity by 10–20% (8). Sedimentation of IV phenytoin may lead to phlebitis, a condition that must be avoided due to the potential harm to patients (9–12).

Chemical incompatibility in these preparations may arise from changes in functional groups and a reduction in drug concentration (13). Chemical incompatibilities are detected using analytical techniques such as HPLC, FTIR spectroscopy, and UV-Vis spectroscopy (14). Specifically, chemical incompatibility of phenytoin IV can be observed in FTIR testing through deviations in functional group characteristics between the standard and the sample (15,16). Changes in the functional groups within the preparation may lead to toxicity in patients (17,18).

This study distinguishes itself from previous research by focusing on the application of IV phenytoin therapy in clinical settings, where phenytoin is dissolved in normal saline and administered multiple times per day. Residual solution from a previous dose, if within therapeutic limits, may be re-administered in subsequent doses. Given this practice, the present study aims to evaluate the physical and chemical stability of reconstituted IV phenytoin in normal saline at intervals of 0, 3, and 6 hours.

## MATERIALS AND METHODS

### Research design

The study examines the chemical compatibility of IV phenytoin formulations from three manufacturers following reconstitution in normal saline. The physicochemical compatibility assessment includes measurements of pH, particle size, concentration stability, functional groups of the precipitated compounds, and molecular weight.

### Tools and materials

### Research materials

The materials used in this study include IV phenytoin formulations from three different manufacturers (labeled A, B, and C), along with standard phenytoin and normal saline

61 solutions. The equipment includes essential labware, lens tissue, micropipettes, a laminar flow
62 hood, and several analytical instruments: a UV-180 double-beam spectrometer, an FTIR Cary
63 630, a GC 7890B 5977A MSD, a Lutron TU 2016 Turbidity Meter, an Olympus CX23
64 microscope, and a Trans Instruments WalkLAB HP 9010 pH meter.

65 **Research Instruments**

66 **Physical compatibility test of IV phenytoin preparations**

67 **Test pH**

68 The pH of each formulation is measured using a Trans Instruments WalkLAB HP 9010 pH
69 meter. The instrument is calibrated with pH 4 and pH 7 buffer solutions before testing. A 10
70 mL sample is measured, with three replications per test, and observations are made at 0, 3, and
71 6 hours after reconstitution. A change in pH $\geq$ 1 between initial and final measurements
72 indicates physical incompatibility (19,20).

73 **Microscopic test**

74 Microscopic analysis of the IV phenytoin and normal saline mixtures is conducted using an
75 Olympus CX23 microscope. Observations are documented at 0, 3, and 6 hours, with 1 mL of
76 IV phenytoin mixed with 10 mL of normal saline. Each timepoint is documented for each
77 manufacturer, and results are compared.

78

79 **Chemical compatibility test of IV phenytoin by UV spectrophotometry.**

80 **Phenytoin standard testing**

81 The stability of phenytoin concentration is assessed using a UV-180 double-beam
82 spectrometer. A standard solution is prepared by dissolving 50 mg of phenytoin with a drop of
83 propylene glycol in normal saline up to 50 mL (1000 ppm). From this, serial dilutions of 2 ppm
84 to 10 ppm are created, and the absorbance is measured at λ 200–250 nm.

85

86 **Phenytoin sample testing**

87 A 50 mg/mL phenytoin sample is mixed with 10 mL of normal saline, then further diluted with
88 normal saline until an absorbance range of 0.2–0.8 is achieved. After filtering any precipitate,
89 absorbance readings are taken from 0 to 8 hours at λ 200–250 nm.

90

91 **Testing the functional groups of phenytoin IV precipitates using FTIR**

92 The functional groups of phenytoin precipitates were analyzed with an FTIR Cary 630
93 spectrometer. A 1 mL sample of a 50 mg phenytoin preparation was mixed with 10 mL of
94 normal saline. The resulting precipitate was filtered through filter paper, dried, and the
95 crystalline powder was placed on the FTIR prism for spectral analysis.

96

97 **IV phenytoin precipitate confirmation test with GCMS**

98 The precipitate from the IV phenytoin preparation was further analyzed with a GC 7890B
99 5977A MSD for confirmation. Following reconstitution, a 1 mL sample of a 50 mg phenytoin
100 solution was mixed with 10 mL of normal saline. After filtration and drying of the precipitate,
101 1 mg of the crystalline powder was dissolved in 2 mL of methanol. This solution was injected
102 into the GC-MS column to obtain the m/z absorption values of the preparation.

103

104 **Data analysis**

105 The chemical compatibility of IV phenytoin preparations was assessed through a series of tests.
106 UV spectrophotometry measured the % concentration over an 8-hour period, with data
107 presented as a curve to illustrate stability trends. FTIR analysis compared the functional groups
108 of standard phenytoin with those of the precipitate formed after reconstitution in normal saline,
109 highlighting any chemical incompatibilities through spectral and tabular documentation.
110 Molecular weight confirmation via GC-MS involved comparing chromatograms of standard
111 and precipitated phenytoin, identifying any discrepancies. Additionally, physical compatibility
112 was examined through pH measurements at 0, 3, and 6 hours, calculating % changes to gauge
113 stability, while organoleptic tests visually documented physical changes in turbidity or color
114 across the same time points for three phenytoin formulations.

115

116 **RESULTS AND DISCUSSION**

117 **Stability of reconstitution of IV phenytoin in normal saline**

118 The reconstitution of IV phenytoin in normal saline shows instability, as indicated by physical
119 tests across three IV phenytoin samples. Instability was evident through concentration stability
120 tests from t0 to t8, organoleptic microscopy observations of particle size, and pH measurements
121 at t0, t3, and t6.

122

123 **UV Spectrophotometry Test**

124 The stability of IV phenytoin concentration in normal saline was analyzed using UV-Vis
125 spectrophotometry to assess drug concentration over a storage period of 0 to 8 hours.
126 Absorbance measurements of the phenytoin preparation were recorded at a wavelength of
127 203.7 nm. Prior to sample measurement, phenytoin standards at concentrations of 5, 6, 7, 8,
128 and 9 ppm were read, yielding an intercept (a) of -0.2807, a slope (b) of 0.0994, and a
129 correlation coefficient (r) of 0.9985.

130

131 Phenytoin samples were tested following the same procedure as the standards, with 1 ml of IV
132 phenytoin (equivalent to 50 mg) diluted to 7 ppm for readings at hour 0, resulting in absorbance
133 values of 0.466, 0.375, and 0.263 for samples A, B, and C, respectively. By hour 8, a decline
134 in absorbance was observed, with values of 0.312, 0.457, and 0.197 for samples A, B, and C,
135 respectively. The stability of IV phenytoin concentration in normal saline over time is
136 illustrated through % absorbance vs. time data, presented in Figure 1.

137 **Figure 1. Stability of IV Phenytoin Concentration in Normal Saline as Measured by UV**
138 **Spectrophotometry**

139

140 **Table 1. Significant % Absorbance Values at T0 and T8 for IV Phenytoin in**
141 **Normal Saline**

142 The decreased stability of IV phenytoin in normal saline is attributed to precipitate formation
143 during testing. Phenytoin's crystalline precipitation is primarily due to the high water content
144 in reconstitution, as phenytoin exhibits greater stability in propylene glycol than in water. In
145 normal saline, propylene glycol binds strongly with water, which induces phenytoin
146 precipitation and subsequently lowers its concentration. This decline is observed through UV-

Vis spectrophotometry, which measures the absorbance of dissolved compounds in the liquid phase.

## Microscopic Observation of Phenytoin Preparation in 0.9% Normal Saline

**Figure 2. Microscopic Observations of Phenytoin Preparations**

Figure 2 displays particle size assessments from the organoleptic test of reconstituted IV phenytoin in normal saline for samples A, B, and C. Observed with an Olympus CX23 microscope at 10x40 magnification, the results reveal initially small, evenly dispersed crystals at t0. Over time, the crystals grow larger, leading to precipitation. This phenomenon was corroborated by organoleptic tests on crystal particles at t0, t3, and t6.

## Test the pH of Phenytoin preparations in normal saline

## pH Testing of Phenytoin Preparations in Normal Saline

The pH stability of reconstituted phenytoin preparations in normal saline (samples A, B, and C) was evaluated at t0, t3, and t6 hours. The analysis focused on the % increase in pH over time, with results summarized in Table 2.

**Table 2. Physical Stability of pH in IV Phenytoin Preparations**

**Figure 3. Percent Increase in pH of IV Phenytoin in Normal Saline**

Table 2 presents the pH stability test results for IV phenytoin in normal saline, showing the % increase in pH across samples A, B, and C. Notably, the % increase in pH remains below 1 at t0, t3, and t6. For Sample A, the % increase from t0 to t6 is 0.887, and from t3 to t6, it decreases to -0.486. For Sample B, the % increase from t0 to t6 is 0.68, while from t3 to t6, it slightly drops to -0.096. Sample C displays a % increase of -2.908 from t0 to t6 and -1.626 from t3 to t6.

## FTIR Confirmation of Phenytoin Precipitate Identity

## Functional Group Analysis of IV Phenytoin Reconstitution in Normal Saline Using FTIR

To confirm the identity of the precipitate, the functional groups of pure phenytoin were analyzed using FTIR. The FTIR spectra of raw phenytoin show characteristic peaks at 1688 $cm^{-1}$ for the C=O amide group, 736 $cm^{-1}$ for the C-H phenyl group, 1590 $cm^{-1}$ for the N-H amide group, 1292 $cm^{-1}$ for the C-N amide group, and 1569 $cm^{-1}$ for the C=C phenyl group. Figure 4 presents the FTIR spectrum for the phenytoin standard.

**Figure 4. FTIR Spectrum of Standard Phenytoin**

**Figure 5. FTIR Spectrum for Sample A**

**Figure 6. FTIR Spectrum for Sample B,**

**Figure 7. FTIR Spectrum for Sample C**

Readings of the functional groups in the crystalline deposits from IV phenytoin reconstituted in normal saline were obtained from filtering and drying the precipitate. Table 3 summarizes the FTIR absorbance and functional group data, showing chemical bonds/functional groups present in the precipitate of IV phenytoin reconstitution in normal saline.

**Table 3. FTIR Absorbance, Chemical Bonding/Functional Groups of IV Phenytoin Reconstitution Precipitate in Normal Saline**

The IR spectra of crystals obtained from the IV reconstitution of phenytoin in normal saline reveal mean absorption peaks for three samples: 1752 $cm^{-1}$ (C=O amide group), 744 $cm^{-1}$ (C-H phenyl group), 1639 $cm^{-1}$ (N-H amide group), 1286 $cm^{-1}$ (C-N group), and 1504 $cm^{-1}$ (C=C phenyl group). Previous research has documented shifts in these peaks for the C=O amide (1–17 $cm^{-1}$), N-H amide (35 $cm^{-1}$), C-N amide (47 $cm^{-1}$), and C=C phenyl groups (54–88 $cm^{-1}$) . Figures 5, 6, and 7 display the spectra for the phenytoin precipitate samples A, B, and C, which exhibit matching spectral values with the phenytoin standard, confirming their identity as phenytoin.

**GC-MS Confirmation of Precipitate Identity**

198 The molecular weight of the reconstituted phenytoin IV preparations, specifically samples A,
199 B, and C, was assessed using a GC 7890B 5977A MSD system. The precipitate obtained from
200 the reconstitution process was dissolved in 2 ml of methanol for analysis. The resulting
201 chromatograms for the standard and the three samples are presented in Figure 8.

202 **Figure 8. Chromatogram of phenytoin**

203 The standard chromatogram and the chromatograms of the three samples exhibited a
204 consistent m/z value of 180.1, confirming that the precipitate obtained from the reconstitution
205 of intravenous (IV) phenytoin samples A, B, and C in normal saline is indeed phenytoin.

206 The IV reconstitution of phenytoin in normal saline significantly impacted the stability
207 of the preparation's concentration throughout the testing period, as evidenced by the observed
208 decrease in concentration levels across all three samples. This decline can be further
209 contextualized by the FTIR analysis of standard phenytoin presented in Figure 3. The reduction
210 in concentration was attributed to the formation of a precipitate from the IV phenytoin mixture
211 in normal saline. Confirmation of the identity of the resulting precipitate was achieved through
212 FTIR and GC-MS analyses, both of which yielded functional groups with absorbance values
213 consistent with those of the phenytoin standard. The sedimentation analysis of the three
214 samples revealed average absorption peaks at 1752 $cm^{-1}$ for the amide C=O functional group,
215 744 $cm^{-1}$ for the phenyl C-H group, 1639 $cm^{-1}$ for the amide N-H group, 1286 $cm^{-1}$ for the C-
216 N group, and 1504 $cm^{-1}$ for the phenyl C=C group, all confirming a molecular weight of 180.1.

217 Previous investigations (14) utilizing UV spectrophotometry to assess phenytoin
218 preparations have indicated differing methodologies; notably, one study involved dissolving
219 phenytoin injections in water, which contrasts with the current research employing normal
220 saline, the solvent commonly used in clinical settings. Furthermore, FTIR studies of crystalline
221 phenytoin preparations in alcohol have shown that the structural integrity of the sample did not
222 differ significantly from that of the standard (13,15,21). In the present study, the IV phenytoin
223 preparations mixed with normal saline exhibited immediate particle formation, leading to
224 decreased chemical stability of the preparation's concentration. Thus, it can be concluded that
225 phenytoin preparations in normal saline are inherently unstable.

226 Phenytoin is a widely prescribed medication for the management of epilepsy (11,22).
227 The intravenous administration of phenytoin is associated with potential complications,
228 including inflammation and discomfort in the blood vessels (23–25). The stability of
229 intravenous (IV) phenytoin preparations in normal saline may be compromised due to
230 phenytoin's propensity to dissolve in propylene glycol. It is common practice in hospital

settings to dissolve IV phenytoin therapy in normal saline, which consists of 0.9% NaCl, with water serving as the primary solvent. The affinity between water and propylene glycol can lead to the precipitation of phenytoin when reconstituted in normal saline.

Phenytoin possesses a pKa value of 8.3 within its hydantoin structure, necessitating dissolution in an alkaline solvent with a pH of 12 for effective liquid preparations (7,26–31). As indicated in Table 1, there were no significant changes in pH during the study at time points T0, 3, and 6, suggesting a stable environment. Nevertheless, phenytoin tends to precipitate when dissolved in substantial volumes of infusion solutions, primarily due to the pH discrepancy between phenytoin and normal saline (32). To address the challenges associated with administering phenytoin in unstable IV preparations, fosphenytoin—a prodrug of phenytoin—has been developed as a more stable alternative in aqueous solutions. Fosphenytoin contains a modified methoxy group (phosphonoxy) and is metabolically activated by alkaline phosphatase within the body (33,34)

## RESEARCH LIMITATIONS

This study utilized three phenytoin samples from different manufacturers, which may not adequately represent the overall stability and miscibility of phenytoin preparations in normal saline. A larger sample size is necessary to comprehensively assess the incompatibilities that may arise in commercially available IV phenytoin preparations.

## CONCLUSION

The reconstitution of IV phenytoin from various manufacturers can influence the compatibility of the preparation, potentially attributable to the differing additional ingredients or excipients utilized by each manufacturer. The observed instability of IV phenytoin is evidenced by the formation of precipitates, which adversely affects the concentration of the preparation and may hinder the achievement of optimal therapeutic outcomes. To mitigate this issue, healthcare professionals may consider substituting the IV phenytoin preparation with its prodrug, fosphenytoin.

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265 the equipment necessary for sample testing.

266

267 **CONFLICT OF INTEREST**

268 The authors declare that there are no conflicts of interest to disclose.

269

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378
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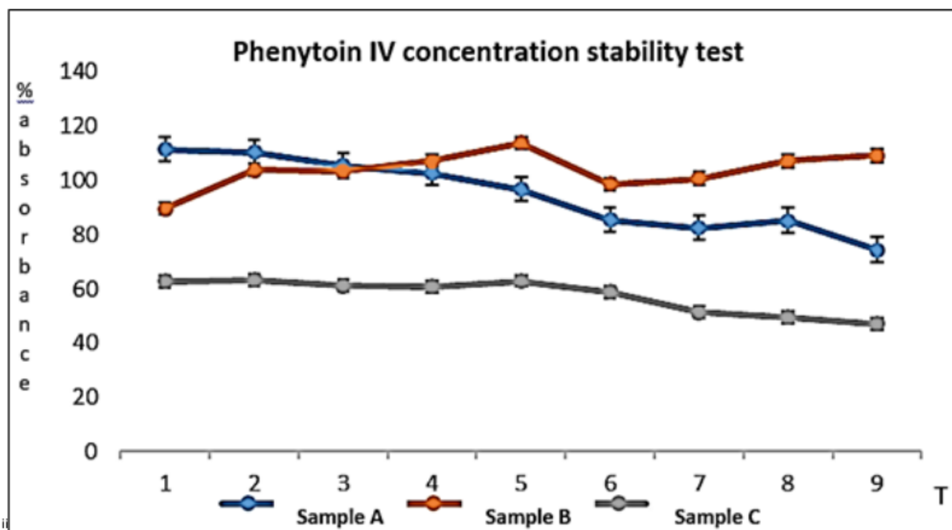
380 **Table and figure**

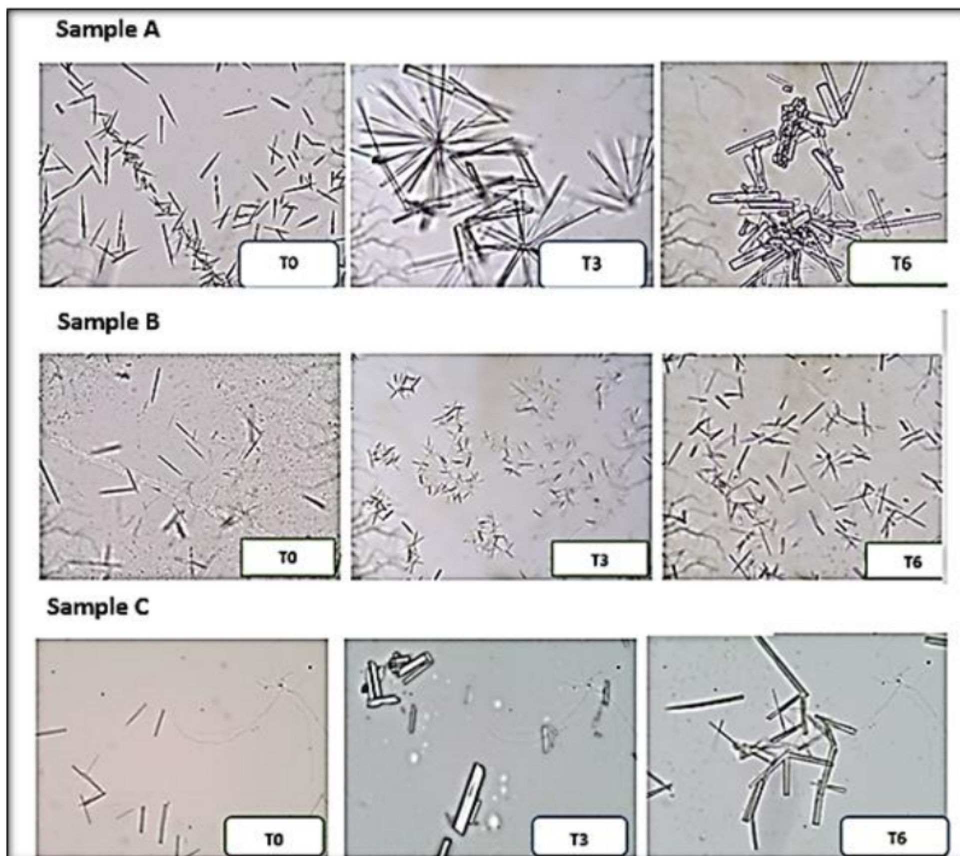



Description: Stability testing of 1 ml iv phenytoin concentration in 10 ml normal saline using UV spectrophotometer on 3 iv phenytoin preparations from different manufacturers at a wavelength of 203.7 nm. The test was carried out every hour for 8 hours. T1 in the figure indicates hour 0 and T9 indicates hour 8.

**Figure 1. Stability of IV Phenytoin Concentration in Normal Saline as Measured by UV Spectrophotometry**

**Table 1. Significant % Absorbance Values at T0 and T8 for IV Phenytoin in Normal Saline**

| Sample | T0 | | | T8 | | | Signif |
|---|---|---|---|---|---|---|---|
| | R1 | R2 | R3 | R1 | R2 | R3 | |
| A | 110.740 | 112.649 | 110.263 | 78.52 | 70.167 | 74.463 | 0.007 |
| B | 91.647 | 86.635 | 90.215 | 106.921 | 108.831 | 111.217 | 0.012 |
| C | 61.814 | 67.303 | 59.189 | 49.881 | 47.494 | 43.914 | 0.021 |

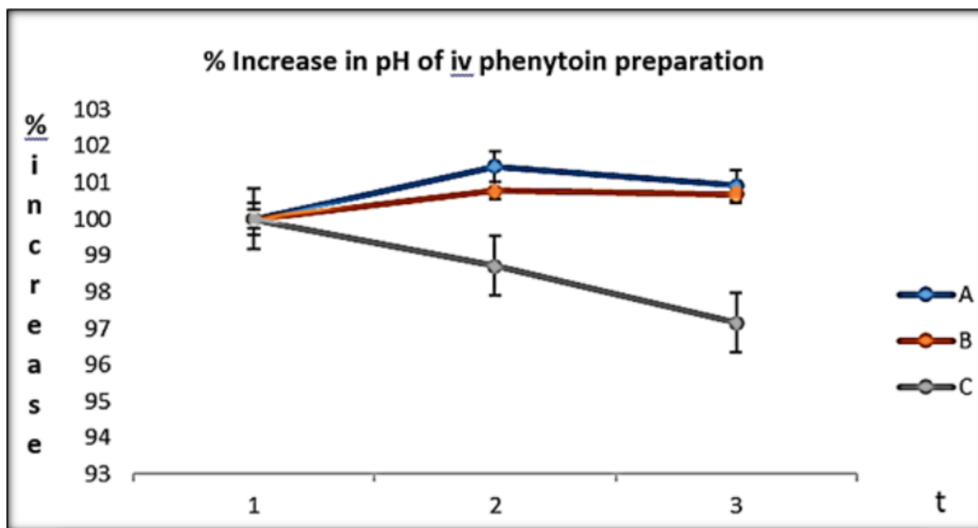



Description : Microscopic image of reconstitution of iv phenytoin preparation in normal saline with a ratio of 1:10 at 40x magnification. Particles were observed at 0, 3, and 6 hours. T0 indicates observation at 0 hours, T3 indicates observation at 3 hours and T6 indicates observation at 6 hours.

**Figure 2. Microscopic Observations of Phenytoin Preparations**

**Table 2. Physical Stability of pH in IV Phenytoin Preparations**

| Sample | % increase pH | | |
|---|---|---|---|
| | T0 | T3 | T6 |
| A | 100 | 101.45 | 100.92 |
| B | 100 | 100.78 | 100.68 |
| C | 100 | 98.72 | 97.15 |




Description: Test of % increase in pH of 1 ml iv phenytoin preparation in 10 ml normal saline. pH was tested for 6 hours, divided into 3 times. Where T0 is hour 0, T2 is 3 hours, and T3 is 6 hours after reconstitution.

**Figure 3. Percent Increase in pH of IV Phenytoin in Normal Saline**

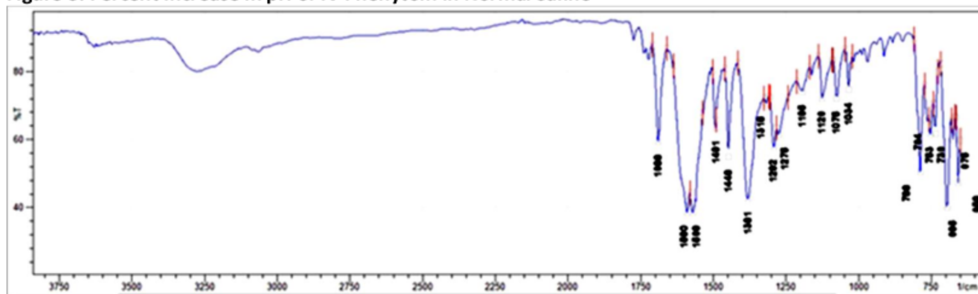


**Figure 4. FTIR Spectrum of Standard Phenytoin**

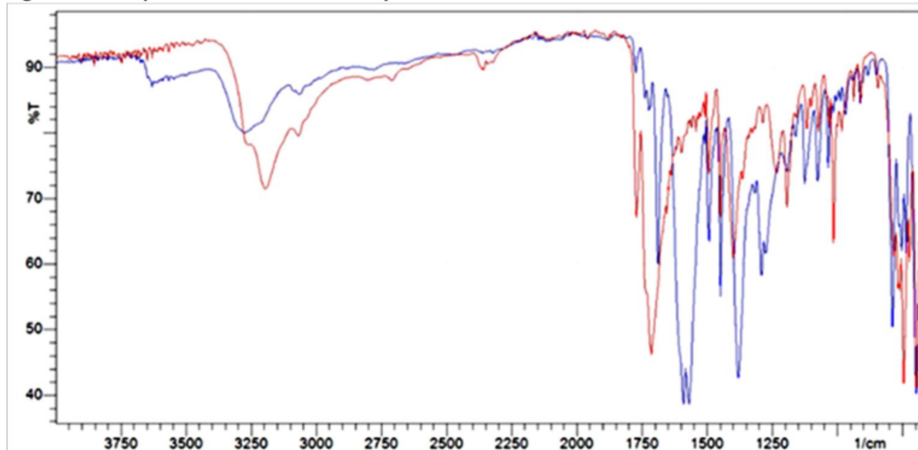



**Figure 5. FTIR Spectrum for Sample A**

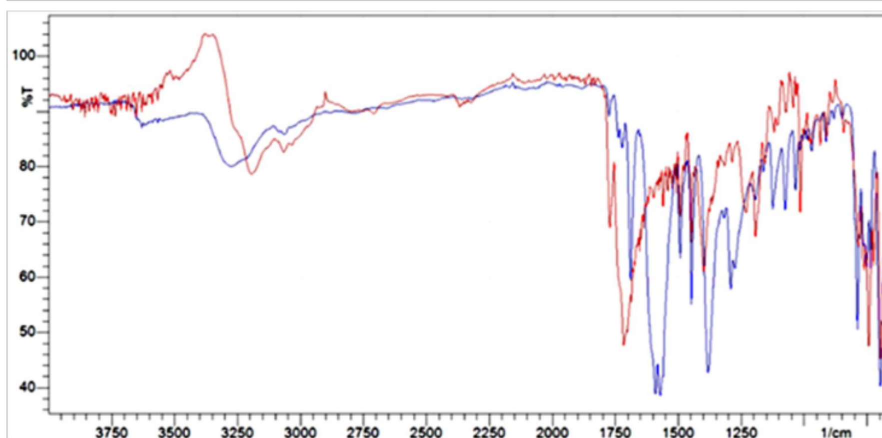


**Figure 6. FTIR Spectrum for Sample B,**

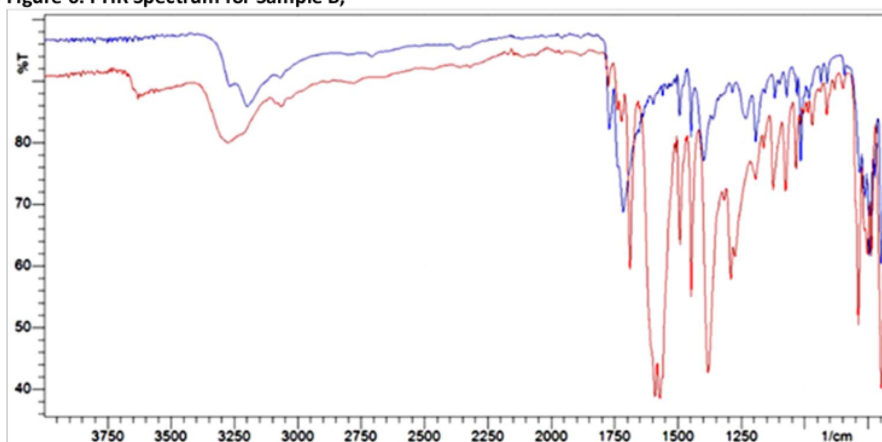
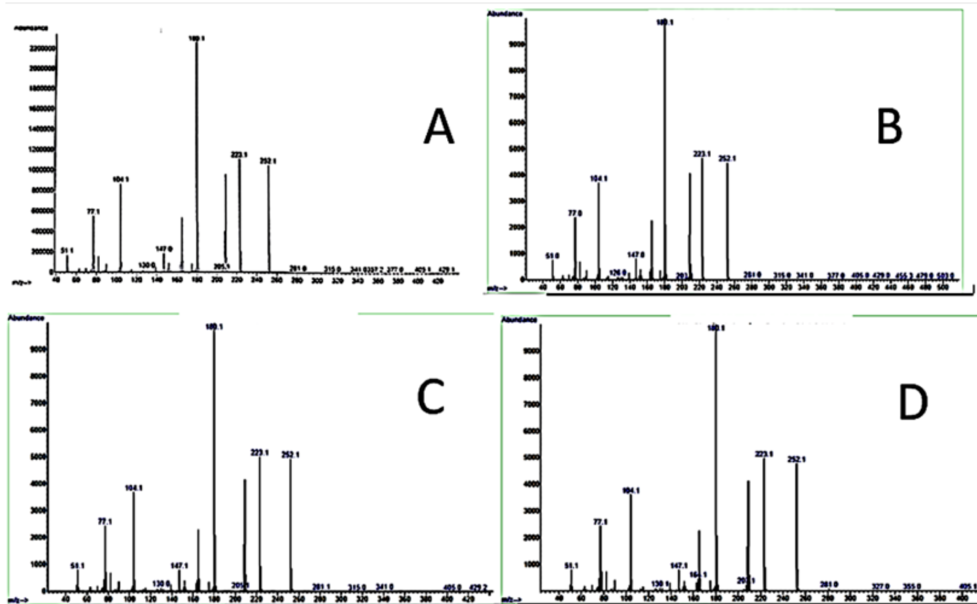


**Figure 7. FTIR Spectrum for Sample C**

**Table 3. FTIR Absorbance, Chemical Bonding/Functional Groups of IV Phenytoin**

| Fuctional group | Chemical bond | TIPE VIBRASI | PUNCAK YANG DIAMATI ($cm^{-1}$) | Observed Peak Sample A ($cm^{-1}$) | Observed Peak Sample B ($cm^{-1}$) | Observed Peak Sample C ($cm^{-1}$) |
|---|---|---|---|---|---|---|
| Amide | C=O | Stretching | 1680-1699 | 1770 | 1716 | 1770 |
| Phenyl | C-H | Stretching | 730-769 | 744 | 744 | 744 |
| Amide | N-H | Bending | 1500-1649 | 1597 | 1684 | 1636 |
| Amide | C-N | Stretching | 1280-1349 | 1233 | 1396 | 1231 |
| Phenyl | C=C | Stretching | 1580 | 1492 | 1526 | 1494 |




**Description: In the GC test image, A is the phenytoin standard, B is sample A, C is sample B and D is sample C.**

**Figure 8. Chromatogram of phenytoin**

# Compatibility test of intravenous preparations of phenytoin

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