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Original Research Article

Physical and Chemical Compatibility Testing of Intravenous Phenytoin Preparations In 0.9% Normal Saline Solution

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ABSTRACT

Intravenous (IV) phenytoin sodium preparations have high pH values (>12) and present compatibility problems with admixtures. Hence, it is necessary to dissolve it in normal (0.9% w/v) saline to adjust the pH to avoid incompatibilities with other medicines, stability, and prevent phlebitis. This study aims to determine the physical and chemical incompatibility of IV phenytoin preparations in normal saline over a certain period. Physical testing of IV phenytoin in normal saline, including organoleptic particle size and pH measurements at 0, 3, and 6 hours. Chemical stability testing was carried out by measuring the concentration of the preparation for 8 hours using a UV spectrophotometer, testing the functional groups of phenytoin IV precipitates in normal saline using FTIR and molecular weight using GC-MS. The results of testing the concentration of phenytoin samples A, B, and C showed instability in the preparations. In the FTIR test, the sample showed absorption bands at 1752 cm^{-1} for the amide (C=O) functional group, 744 cm^{-1} for the phenyl C-H group, and 1286 cm^{-1} for the C-N group. Results of the physical characteristics test showed no increase in pH of more than 1 unit from 0, 3, and 6 hours for the three samples tested, but there was an increase in turbidity of the preparation from visual observation. The MS analysis showed that the pure phenytoin and the precipitated preparation have the same molecular weight of 252.1 m/z.

Keywords: Phenytoin, Dosage concentration, Functional groups, Particle size, pH

Introduction

Intravenous (IV) preparations widely used in hospitals include phenytoin.[1–3] Phenytoin is used in seizures.[4] IV phenytoin is often used by dissolving it in a normal saline solution, but becomes unstable afterwards.[5-6] The instability of phenytoin can cause chemical and physical incompatibility.[7] This is worth attention because it can affect the therapy outcome. The reconstitution of IV phenytoin requires attention to pH, turbidity, and particle size. Phenytoin preparations have a pH of 10-12[5], and normal saline has a pH of 5-7. High differences in pH can cause precipitation.[8] Mixing IV phenytoin in KA-EN 1B can increase turbidity by 10-20%.[9] IV sedimentation can cause phlebitis, which must be prevented due to its harmful effects on IV phenytoin patients.[10–13]

Chemical incompatibility of preparations can occur due to changes in functional groups and a decrease in the concentration of the preparation.[14]

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Detection of chemical incompatibilities is carried out using various tools, including HPLC, FTIR spectrophotometry, UV-Vis spectrophotometry, and others.[15] The finding of chemical incompatibility of phenytoin IV in the FTIR test can be seen by the difference in the functional group of the preparation between the standard and the sample.[16,17] The presence of changes in the functional groups of this preparation mixture can result in toxicity in patients.[18,19] This research was done by mixing phenytoin injection preparations with a normal saline solution. Mixing was carried out according to the instructions provided in the hospital (a ratio of 1 mL of phenytoin dissolved in 10 mL of normal saline). There are 2 objectives of this study. The first was to determine the stability of the reconstituted phenytoin preparations within 0 to 360 minutes from a physical perspective using a microscope. This test was used to observe the crystals formed from mixing phenytoin preparations in normal saline at a specific time, and the pH of the preparation was also measured. Secondly, the decrease in concentration at 0 to 8 hours, functional groups, and molecular weight of the precipitate were also evaluated.

Materials and Methods

Research design

Experiment on chemical compatibility of IV phenytoin preparations, samples obtained from reconstitution of 3 manufacturers' preparations with normal saline solution. Physicochemical compatibility tests were carried out by looking at pH, particle size, concentration stability, functional groups of the preparation precipitate, and molecular weight.

Materials

The materials used include IV phenytoin preparations from 3 manufacturers (A, B, C), standard phenytoin, and normal saline preparations. Other materials include glassware, lens tissue,

micropipette, laminar air flow, double beam spectrophotometer model (UV-180) manufacturer Shimadzu made in Japan, FTIR model Cary 630 manufacturer Agilent made in India, GC model 7890B 5977A MSD manufacturer Agilent made in America, Turbidity meter model TU 2016 merk Lutron made in Taiwan, microscope model Olympus CX23 made in Japan and pH meter model Trans Instruments WalkLAB HP 9010 from Singapore.

Physical compatibility test of IV phenytoin preparations

pH test

The test used a Trans Instruments WalkLAB HP 9010 pH meter. The test was carried out by calibrating the pH meter using pH 4 and 7 buffers. After the instrument was calibrated, the test sample was measured with a volume of 10 mL in one test and replicated 3 times. Observations were made at 0, 3, and 6 hours of mixing the preparation, and the results were declared physically incompatible if the initial and final pH were ≥1 different.[20,21]

Organoleptic test

Organoleptic testing of a mixture of IV phenytoin preparations in normal saline using an Olympus CX23 microscope was done. The visual observations were carried out at 0, 3, and 6 hours by mixing 1 mL of IV phenytoin in 10 mL of normal saline, and the results were recorded and compared from the three factories.

Chemical compatibility test of IV phenytoin by UV spectrophotometry.

Phenytoin standard testing

The stability of phenytoin concentrations was determined using a double-beam spectrophotometer (UV-180). Firstly, a standard phenytoin solution was prepared by weighing and mixing phenytoin (50 mg), propylene glycol 1 drop, and 50 mL of normal saline (1000 ppm). A concentration of 2 ppm-10 ppm was made from the standard solution, and the absorbance was read at 200-250 nm using a UV-spectrophotometer.

Phenytoin sample testing

Phenytoin (50 mg) preparation (1 mL) was mixed with normal saline (10 mL). The mixture was diluted with normal saline until an absorbance of 0.2-0.8 was obtained. The precipitate formed was filtered, and the absorbance of the filtrate was measured using a UV-spectrophotometer at 0 to 8 hours at 200-250 nm.

Functional groups Test of phenytoin IV precipitates using FTIR

The functional groups of phenytoin precipitates were determined using FTIR Cary 630. Briefly, 1 mL of phenytoin preparation (50 mg) and 10 mL of normal saline were mixed. The precipitate from the preparation mixture was filtered using filter paper and dried. The precipitate crystals were measured using an FTIR prism.

IV phenytoin precipitate confirmation test with GC-MS

In this assay, 1 mL of phenytoin preparation (50 mg) was mixed with 10 mL of normal saline. The precipitate from the preparation mixture was filtered using filter paper and dried. 1 mg of the precipitated crystalline powder was mixed with 2 mL of methanol and injected into the GC-MS column. The m/z absorption value of the preparation was obtained using an Agilent GC-MS 7890B 5977A MSD.

Data analysis

The chemical compatibility of IV phenytoin preparations was determined using UV spectrophotometry by comparing the % concentration at T (time) 0 to 8 hours, presented as a curve. Functional groups were determined using FTIR by comparing the differences in the standard phenytoin FTIR spectrum with the precipitate resulting from the reconstitution of the phenytoin preparation with normal saline, presented in tabular and spectral form. Molecular weight was determined using GC-MS by comparing the phenytoin standard m/z value with the reconstituted precipitate presented in the overlapping chromatogram. A physical test of the pH of the mixture of phenytoin preparations in normal saline was done by calculating the % increase and organoleptic testing of the mixture by comparing the images of the three mixtures of phenytoin in normal saline from T (time) 0, 3, and 6 hours.

Results and Discussion

In the stability studies of reconstituted IV phenytoin in normal saline, the results showed that the reconstituted preparations were unstable, as demonstrated by the physical tests on the three samples of IV phenytoin preparations. This was evident from the concentration stability test at 0 to 8 hours, organoleptic microscope data on particle size, and pH at 0, 3, and 6 hours. The main objective of testing the stability of IV phenytoin concentration in normal saline using UV-Vis spectrophotometry is to determine the concentration of IV phenytoin drug within a storage time of 0 to 8 hours. The absorbance reading of the phenytoin preparation was recorded at a wavelength of 203.7 nm. A standard preparation of phenytoin at concentrations of 5 ppm, 6 ppm, 7 ppm, 8 ppm, and 9 ppm was utilised to generate standard plots, and the following values were obtained: intercept= -0.2807, b (slope) 0.0994 and r (correlation) 0.9985. Similarly, the phenytoin test samples were evaluated as the standard phenytoin treatment. 1 mL IV phenytoin preparation is equivalent to 50 mg. The absorbance reading of the preparation was carried out at a concentration of 7 ppm at hour 0, and the absorbance values obtained for samples A, B, and C, respectively, were 0.466, 0.375 and 0.263. At the 8th hour, the absorbance results of the reconstituted preparation decreased to 0.312, 0.457, and 0.197 for A, B, and C, respectively. The stability of IV phenytoin concentration in normal saline is presented in the % absorbance vs T data in Figure 1. The decreased stability of IV phenytoin preparations in normal saline was due to the formation of precipitates during the testing process. The precipitation of phenytoin crystals was due to a more extensive water phase in the reconstituted preparation. Phenytoin is unstable in water and more stable in propylene glycol. Propylene glycol binds with the water contained in normal saline. The strong bond between water and propylene glycol causes phenytoin to precipitate. This instability causes a decrease in the concentration of the preparation and the spectrophotometric reading of the absorbance of the compounds dissolved in the liquid phase.

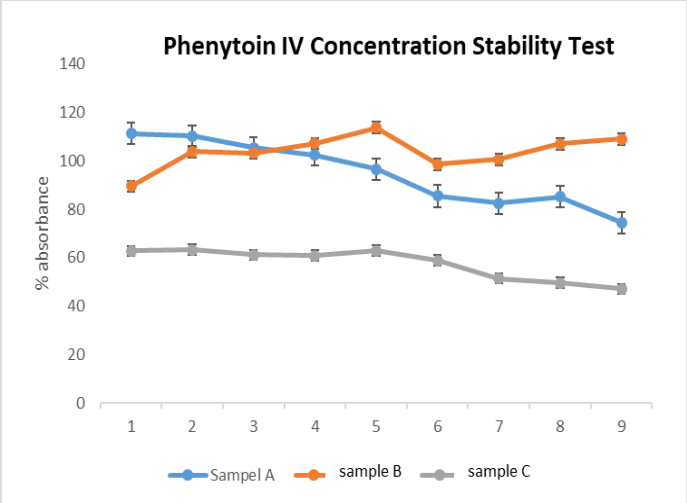

Figure 1: Stability of Phenytoin IV Concentration In Normal Saline Using UV Spectrophotometry

Description: Stability testing of 1 mL iv phenytoin concentration in 10 mL normal saline using a 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.

The organoleptic test of particle size resulting from the reconstitution of IV phenytoin preparations for samples A, B, and C in normal saline is presented in Figure 2. The particle size of the samples was viewed with an Olympus CX23 microscope using a magnification of 10 x 40

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on the three samples. The crystal formation at time 0 was evenly dispersed in the preparation because the crystal formation was still small. Meanwhile, over a more extended period, the crystal formation becomes larger, and this causes the crystals to precipitate during the preparation. This was confirmed by organoleptic testing of crystal particles at 0, 3, and 6 hours.

The pH of reconstituted phenytoin preparations in normal saline samples A, B, and C was measured 3 times at 0, 3, and 6 hours. The pH test results were analysed using the % increase value vs. time. The result of the % increase in pH is presented in Table 2. The % increase should not exceed 1 at 0, 3, and 6 hours. % increase in pH of sample A at 0 to 6 hours was 0.887 and at 3 to 6 hours -0.486. For sample B, the % increase in pH at 0 to 6 hours was 0.68 and at 3 to 6 hours was -0.096. In contrast, sample C was -2.908 at 0 to 6 hours and -1.626 at 3 to 6 hours.

Table 1: Significant values of % absorbance of T0 and T8 Phenytoin IV in normal saline

Sample	absorbance at 0 hour (%)			absorbance at 8 hours (%)			Significance
	R1	R2	R3	R1	R2	R3	
A	110.40	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

Table 2: Physical Stability of pH of Phenytoin Preparations IV

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

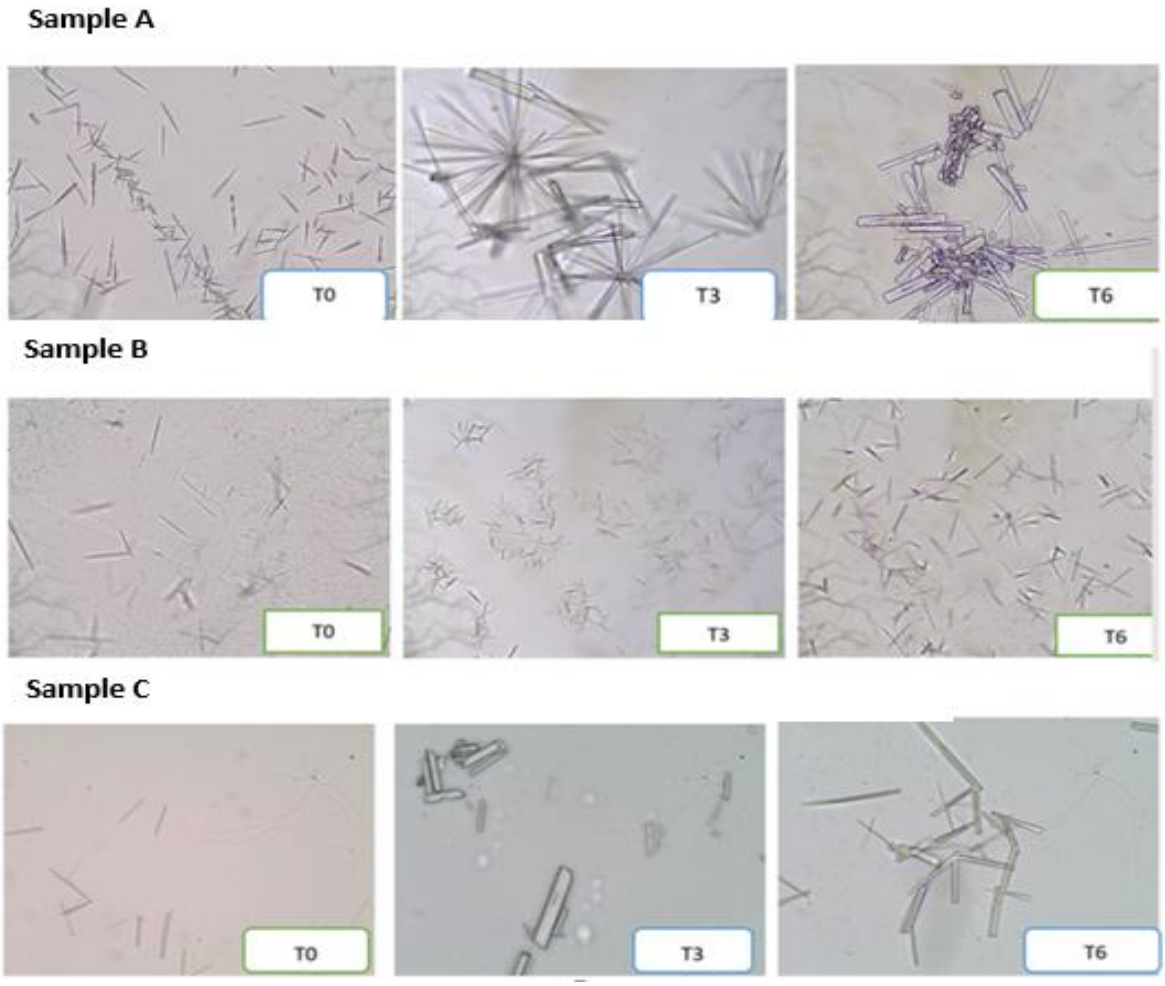

Figure 2: Microscopic features of Phenytoin preparations
Description: Microscopic image of reconstitution of iv phenytoin preparation in normal saline with a ratio of 1:10 at 40x magnification. Particles were observed at 0, 3, and 6 hours. T0 indicates observation at 0 hours, T3 at 3 hours, and T6 at 6 hours.

Testing the chemical structure of pure phenytoin using FTIR was carried out by reading standard solid preparations. From the test results, the FTIR spectra of raw phenytoin showed peaks for the amide group C=O 1688 cm^{-1}, the phenyl C-H group at 736 cm^{-1}, the amide group N-H 1590 cm^{-1}, and the amide group C-N 1292 cm^{-1}. Standard testing for phenytoin with FTIR is shown in Figure 4. Readings of the functional groups of phenytoin IV sample crystal deposits in normal saline were obtained by filtering the dried, reconstituted preparation. The results of the absorbance and functional group readings of the IV phenytoin reconstitution precipitate in normal saline are presented in Table 3. The IR spectrum of crystals resulting from IV reconstitution of phenytoin with normal saline shows the average absorption of the three factories at 1752 cm^{-1} for the Amide C=O functional group, 744 cm^{-1} for the phenyl C-H group, 1639 cm^{-1} amide N-H group, and 1286 cm^{-1} C-N group. Previous research found differences in peak shifts in the C=O amide group between 1-17 cm^{-1}, the N-H amide group 35 cm^{-1}, the C-N bond amide group 47 cm^{-1} .[17] The spectra from the test results for the sediment of samples of phenytoin in normal saline is shown in Figures 5, 6, and 7.

Table 3: FTIR Absorbance, chemical bonding/functional groups of Phenytoin IV reconstitution precipitates and Normal Saline

Functional group	Chemical bond	Vibration type	Observed peaks (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			

Description: The results of the spectra of the precipitate from the reconstitution of IV phenytoin preparations in normal saline in the FTIr test carried out from 3 samples A, B, and C compared to the standard. The functional groups observed include Amide (C=O), Phenyl (C-H), Amide (N-H), Amide (C-N), and Phenyl (C=C).

Table 3 shows the results of the sedimentation test of phenytoin iv reconstitution in normal saline, 4 functional groups were observed, namely amide (C=O), phenyl (C-H), amide (N-H), and imine (C=N). The spectra of sediment samples A, B and C were different from the phenytoin standard, this can be seen in the phenyl functional group (C=C). The phenyl functional group (C=C) observed at 1580 cm^{-1} did not appear in the precipitate of the 3 samples. Due to the difference in the spectra of the functional groups of phenytoin iv sediment in normal saline, sediment testing was carried out with GC-MS to confirm the study results.

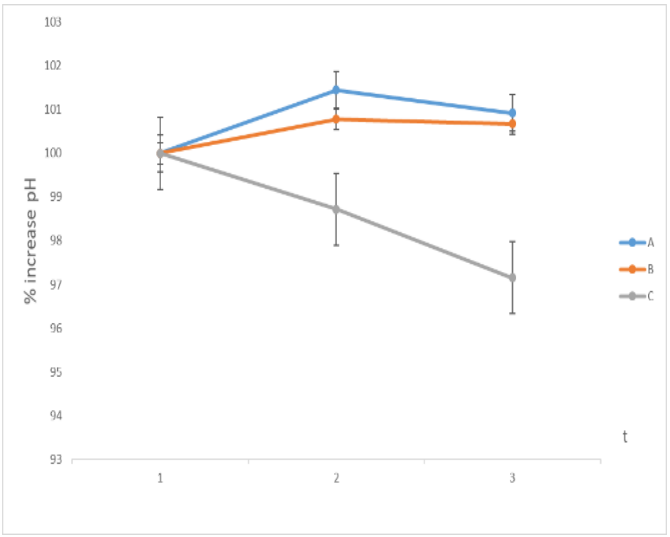

Figure 3: Percent Increase in pH of Phenytoin IV in normal saline

Description: percentage increase in pH in 3 samples within 0, 3, and 6 hours. The pH at 0 hours seen in t1, the pH at 3th hours seen at t2 and at 6th hours seen at t3. The % increase in pH of sample A at the test time can be seen on the blue line, sample B on the red line and sample C on the gray line.

Figure 3 showed the data of % increase in pH from 3 samples IV phenytoin in normal saline. The pH changes from the three samples looks very small around 1%, while incompatibility definition refer to increases of pH by 1 unit (7.1%). Especially on C sample the pH decreases 2.9% in t 0 to 6 hours.

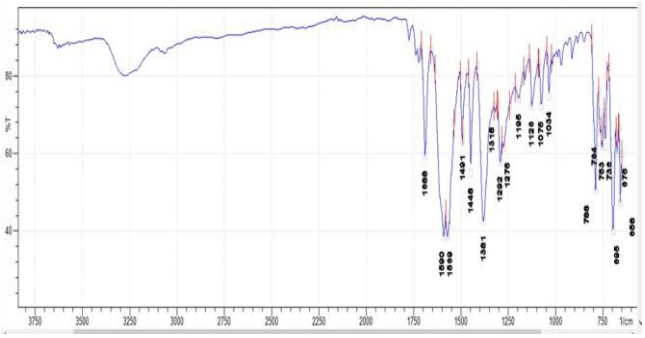

Figure 4: FTIR spectrum of standard phenytoin sample

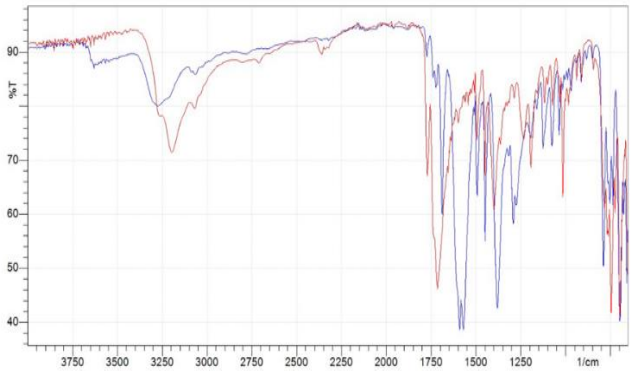

Figure 5: FTIR spectrum of sample A

Description: The spectra formed in blue are the phenytoin standard, and the spectra formed in red are the phenytoin iv sample A precipitate dissolved in normal saline. The precipitate formed is filtered and dried, then read on the FTIR.

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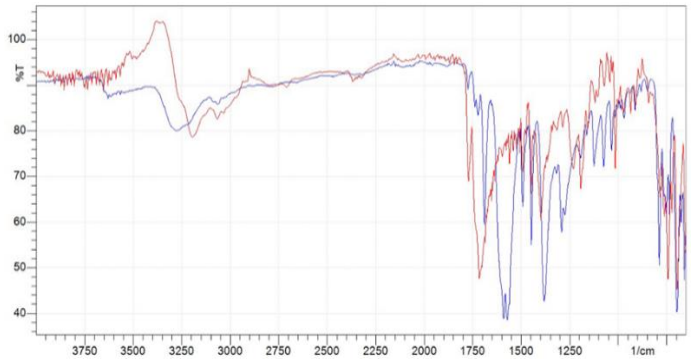

Figure 6: FTIR spectrum of sample B

Description: The spectra formed in blue are the phenytoin standard, and the spectra formed in red are the phenytoin iv sample B precipitate dissolved in normal saline. The precipitate formed is filtered and dried, then read on the FTIR.

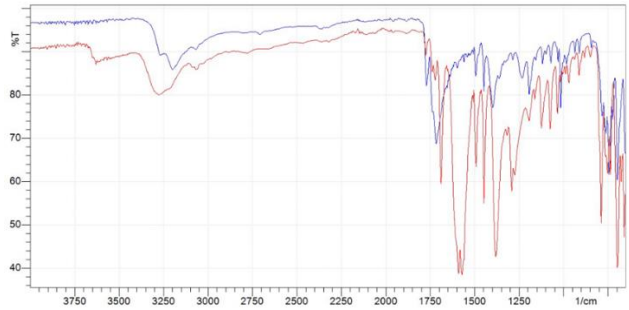

Figure 7: FTIR spectrum of sample C

Description: The spectra formed in blue are the phenytoin standard, and the red is the phenytoin iv sample C precipitate dissolved in normal saline. The precipitate formed is filtered and dried, then read on the FTIr.

The results of reading the reconstituted sediment of samples A, B, and C in normal saline can be concluded as phenytoin because it has the same spectral value as the standard. The molecular weight of the reconstitution results of phenytoin IV preparations, samples A, B, and C, were obtained from the precipitate resulting from the reconstitution dissolved in 2 mL methanol and determined using a GC 7890B 5977A MSD spectrometer. The results of the standard chromatogram and the three samples are presented in Figures 8 to 12. The standard chromatogram and the three samples showed the same m/z value 252.1. This confirms that the precipitate obtained from reconstitution in normal saline IV phenytoin samples A, B, and C is phenytoin. The IV reconstitution of phenytoin in normal saline affected the stability of the preparation concentration during the test period. This was seen in decreased concentration levels of the three preparation samples used. The formation of a precipitate from the IV phenytoin mixture in normal saline caused the decrease in concentration. A confirmatory test of the resulting precipitate was done using FTIR and GCMS, where both tests produced functional groups with the same absorbance value as the phenytoin standard. The sedimentation of the three samples produced an average absorption from the three factories of 1752 cm^{-1} for the Amide C=O functional group, 744 cm^{-1} for the phenyl C-H group, 1639 cm^{-1} for the Amide N-H group, 1286 cm^{-1} for the C-N group, and 1504 $cm\text{-}^{1}$ phenyl group C=C and has the same molecular weight 252.1. A similar work on testing phenytoin preparations using UV spectrophotometry has been reported.[15] In this research, the phenytoin injection was dissolved in water, which differs from the current research. Testing of crystalline phenytoin preparations in alcohol using FTIR has also been studied, and results were not different between the functional groups of the sample and the standard.[14,16,22] The current research uses normal saline, the solvent used for hospital therapy. In this study, IV phenytoin preparations in normal saline at 0 hours showed particle formation, and the chemical stability of the preparation concentration decreased. It can be concluded that phenytoin preparations in normal saline are unstable. Phenytoin is one of the drugs widely prescribed for epilepsy.[12,23] Intravenous administration is known to cause inflammation and pain in blood vessels.[24–26] The stability of IV phenytoin preparations in normal saline can be disturbed due to the tendency of phenytoin to dissolve in propylene glycol. A common occurrence in hospitals is IV phenytoin therapy is dissolved in normal saline. Normal saline contains 0.9% NaCl dissolved in water as the preparation solvent. Water and propylene glycol are the main solvents for phenytoin, and the two solvents bind very easily, which causes the reconstitution of phenytoin in normal saline to precipitate. Phenytoin has a pKa value of 8.3 in the hydantoin part. In liquid preparations, this must be dissolved in an alkaline solvent (pH 12).[7,27–31] When phenytoin is dissolved in a large amount of infusion solution, it will precipitate.[32,33] Fosphenytoin is a prodrug of phenytoin that is stable in water, so it can be used to solve the problem of administering phenytoin in unstable IV preparations. Fosphenytoin is phenytoin but with a substitution in the methoxy group (phosphonoxy) and is metabolically activated by alkaline phosphatase in the body.[34,35] A drawback of this study is that it used 3 phenytoin samples from different manufacturers, which cannot represent the stability of the miscibility of the preparation in normal saline. Large samples are still needed to determine the incompatibilities of IV phenytoin preparations on the market.

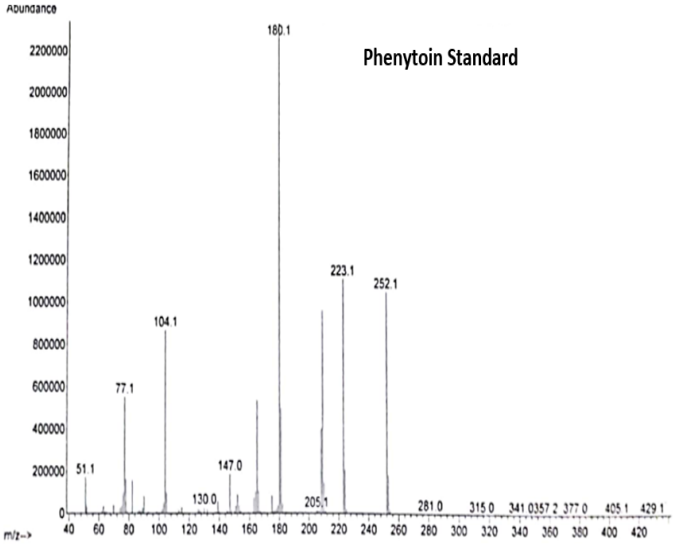

Figure 8: MS chromatogram of standard Phenytoin

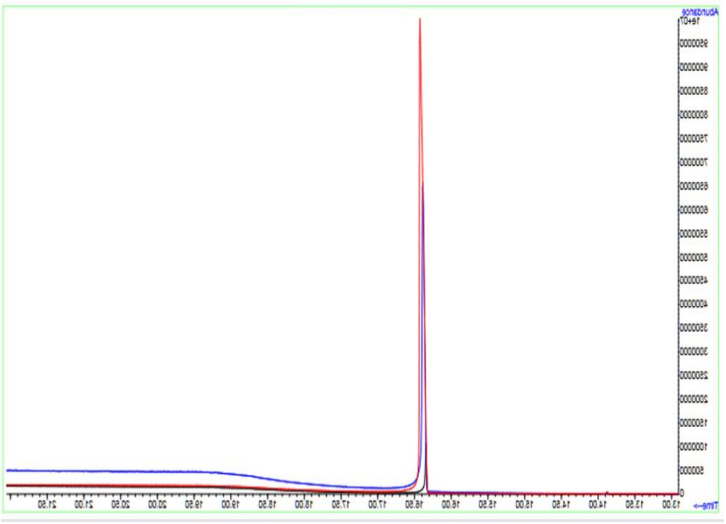

Figure 9: Overlap of standard chromatograms of phenytoin with samples A, B, C

Description: abundance blue sample A, red sample B, black sample C

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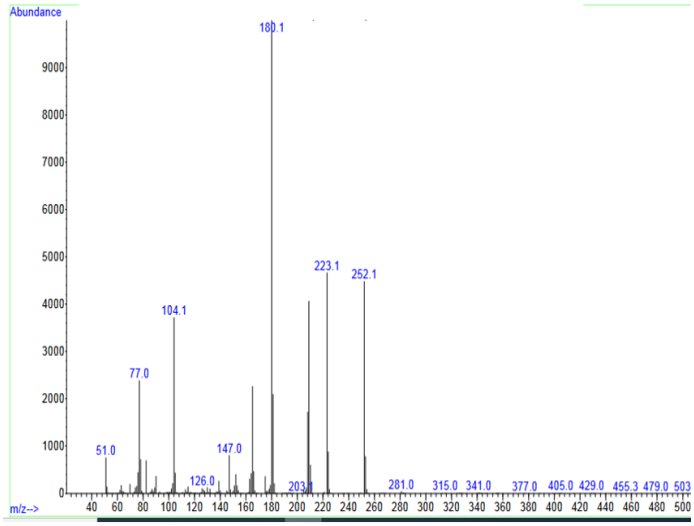

Figure 10: MS chromatogram of sample A

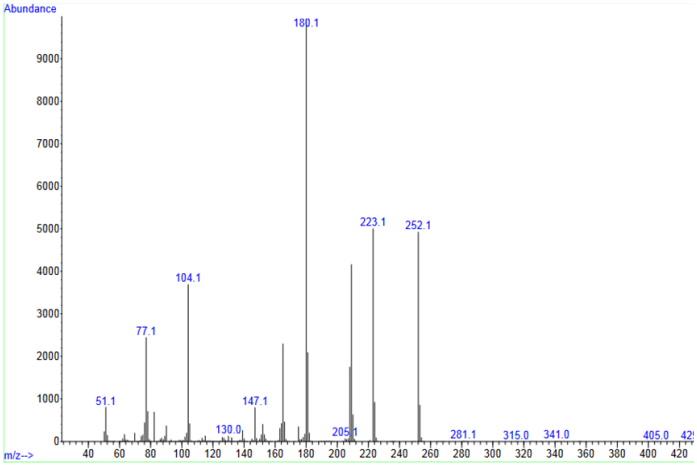

Figure 11: MS chromatogram of sample B

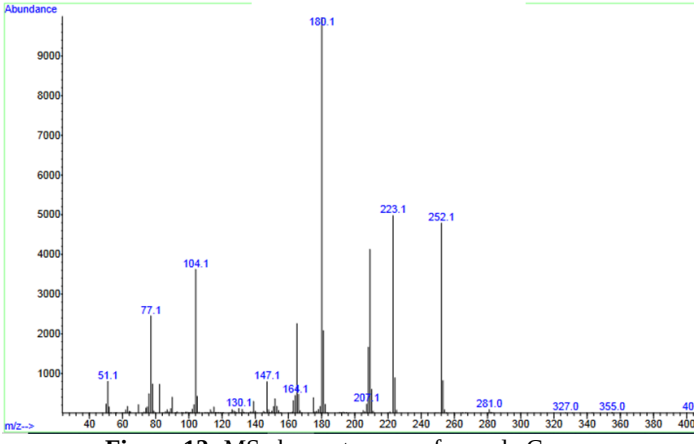

Figure 12: MS chromatogram of sample C

Conclusion

Reconstitution of IV phenytoin from various manufacturers can affect the compatibility of the preparation, which could be due to the additional ingredients/excipients used by each manufacturer. The instability of IV phenytoin can be seen from the formation of precipitates. This reduces the concentration of the preparation; hence, the therapeutic outcome may not be achieved. The problem of instability of IV phenytoin preparation can be solved by replacing the IV phenytoin preparation with the prodrug, Fosphenytoin.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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