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PH-Dependent Solubility and UV–Visible Spectrophotometric Analysis of Isotretinoin in Various Dissolution Media

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Abstract:

Solubility is an important factor influencing the oral bioavailability of poorly water-soluble drugs such as isotretinoin. In this study, the pH-dependent solubility and spectrophotometric characteristics of isotretinoin were evaluated in different media (pH 1.2, 5.8, 6.8, and 7.4). The λmax was determined using UV–Visible spectroscopy, and calibration curves in all media showed good linearity, confirming the reliability of the method.

Saturated solubility studies revealed that isotretinoin has very low solubility in distilled water and acidic conditions, while its solubility increases as the pH rises. The λmax remained nearly unchanged across all pH conditions, indicating that pH does not significantly affect its absorption properties. The increase in solubility at higher pH is due to greater ionization of the drug.

Overall, the results highlight that isotretinoin exhibits pH-dependent solubility, and optimizing pH conditions is essential in formulation development to enhance its solubility and oral bioavailability, as it belongs to the BCS Class II category.

Keywords:

Isotretinoin; Solubility; pH-dependent solubility; UV–Visible spectroscopy; λmax; Calibration curve; Saturated solubility; BCS Class II; Bioavailability

Introduction

Solubility refers to the capacity of a material to dissolve in another substance, resulting in the formation of a solution.[1] The processes of solubility within the human body hold significant importance. Drugs that are poorly soluble in water often exhibit slow absorption rates, which can lead to insufficient and inconsistent bioavailability. Approximately 50% of drugs administered orally face formulation difficulties due to their elevated lipophilicity.[2] To ascertain the most advantageous dissolution conditions, the saturated solubility method was employed, involving the dissolution of the drug in acidic, basic, and distilled water. The quantification of drug solubility was subsequently performed using UV–visible spectroscopy, where absorbance was measured and the Beer–Lambert law was applied.[3] The biopharmaceutical classification system categorizes drugs into four classes: Class I: high solubility and high permeability; Class II: low solubility but high permeability; Class III: high solubility but low permeability; Class IV: low solubility and low permeability. Drugs classified as BCS Class II demonstrate poor solubility yet possess high permeability, a combination that may lead to inconsistent and sometimes reduced bioavailability after oral administration.[4] 13-cis-Retinoic acid (13-cis-RA), commonly known as isotretinoin, is a naturally occurring derivative of vitamin A.[5] Given that 13-cis-retinoic acid is virtually insoluble in aqueous environments, its oral absorption may be affected by the pH of gastrointestinal fluids and the fatty acid composition of the diet. As a result, the pharmacokinetic profile of 13-cis-retinoic acid following oral administration shows significant variability.[6]

Experimental:

Materials:

The isotretinoin was obtained as a complimentary sample from Apionex Pharmaceuticals, Mumbai. Potassium dihydrogen phosphate, sodium hydroxide, and hydrochloric acid were sourced from Research Chem Lab. The distilled water was generated in our research laboratory using a distillation unit.

Determination of λmax of the drug in different dissolution media:

The maximum absorption wavelength (λmax) of the drug was determined in various dissolution mediaIn various dissolution media, including distilled water and buffer solutions with pH levels of 1.2, 5.8, 6.8, and 7.4, a UV–Visible spectrophotometer was utilized. To achieve this, stock solutions of Isotretinoin were individually prepared in each medium. A precise amount of 10 mg of the drug was placed into a 100 mL volumetric flask, and the volume was subsequently adjusted to the mark with the corresponding solvent. The λmax of Isotretinoin in each medium was scanned in spectrum mode across a wavelength range of 200–400 nm, and the associated absorption peaks were documented.

Preparation of standard calibration curves in different media:

Standard calibration curves for Isotretinoin were developed in various dissolution media, specifically distilled water and buffer solutions at pH levels of 1.2, 5.8, 6.8, and 7.4. In this investigation, stock solutions of the drug were prepared separately in each medium. A precisely weighed amount of 100 mg of Isotretinoin was transferred to a volumetric flask, dissolved in 1 mL of methanol, and the volume was then adjusted to the mark with the respective solvent. Subsequent dilutions were made using the same dissolution medium to create solutions of varying concentrations for the construction of the calibration curve. The λmax of the drug in each medium was ascertained using a UV–Visible spectrophotometer.

Determination of saturated solubility:

The saturated solubility of the drug was assessed in distilled water and buffer solutions with pH values ranging from 1.2 to 7.4. For this assessment, 3 mL of distilled water or the corresponding buffer was placed in 5 mL amber-colored glass vials, and an excess quantity of the drug was introduced into each vial, which was then sealed with a stopper. The vials were positioned in an orbital shaking water bath and agitated at 50 rpm for 48 hours, while the temperature was consistently maintained at 37 ± 0.5 °C throughout the experiment. Following equilibration, the samples were filtered through 0.22 µm syringe filters. The filtrates were suitably diluted with the same solvent, and the absorbance was measured using a UV–Visible spectrophotometer. In various dissolution media, such as distilled water and buffer solutions with pH levels of 1.2, 5.8, 6.8, and 7.4, a UV–Visible spectrophotometer was utilized. To achieve this, stock solutions of Isotretinoin were individually prepared in each medium. A precise amount of 10 mg of the drug was placed into a 100 mL volumetric flask, and the volume was subsequently adjusted to the mark with the appropriate solvent. The λmax of Isotretinoin in each medium was scanned (UV-1601PC, Shimadzu Corporation, Japan) at the previously established λmax for the respective medium. The concentration of the drug was determined using the corresponding standard calibration curve created in each solvent.[9-12]

Result And Discussion:

λmax of Isotretinoin in Different Dissolution Media

Figures 3 through 6 and Table 1 illustrate the scanned wavelengths (λmax) of Isotretinoin across various dissolution media. The λmax values were observed to be nearly identical in all media. This indicates that there is no significant alteration in the maximum absorption wavelength of Isotretinoin despite changes in the pH of the dissolution medium.

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T able 1. Scanned λmax values of Isotretinoin in Different Dissolution Media

S. No.	Solvent used for study	Scanned drug λmax (nm)
1	Distilled Water	343
2	Phosphate Buffer pH 1.2	339
3	Phosphate Buffer pH 5.8	339
4	Phosphate Buffer pH 6.8	343
5	Phosphate Buffer pH 7.4	343

UV-Visible spectroscopy

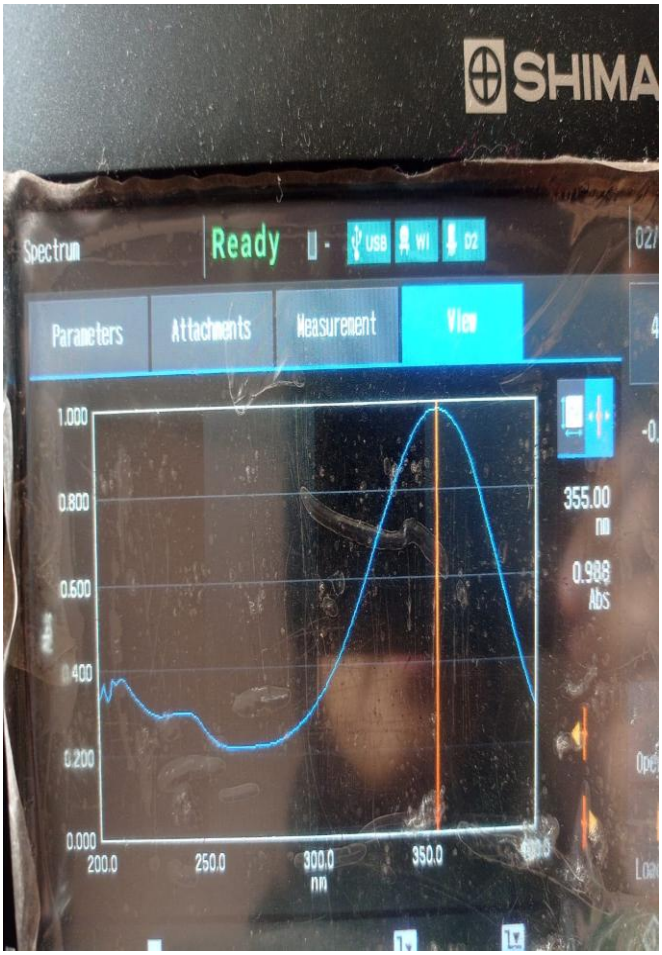

Fig No.1 Lambda max of Isotretinoin

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Calibration Curve of Isotretinoin

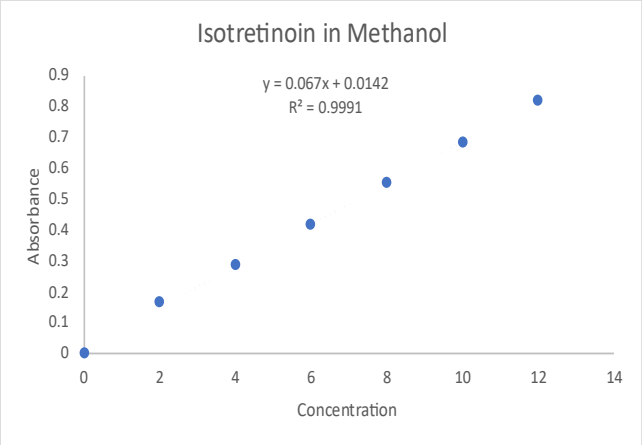

Table no. 2

Conc.	Abs 1
0	0
2	0.165
4	0.288
6	0.416
8	0.549
10	0.683
12	0.817

Fig No. 3 UV drug scanning in Distilled Water

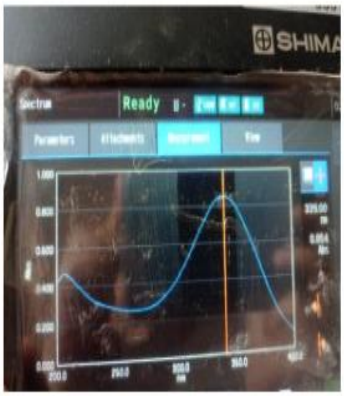

Fig No.4 UV drug scanning in pH 1.2

Fig No. 5 UV drug scanning in pH 5.8

Fig No.6 UV drug scanning in pH 6.8

Fig No. 7 UV drug scanning in pH 7.4

Standard Curve of Isotretinoin in Different Media

Fig. to Fig. show the standard curves of Isotretinoin prepared in different aqueous media. Table 6 presents the linear equations and correlation coefficient (r^2) values for these curves. The results indicate very good correlation coefficients in all media, showing a strong linear relationship between Isotretinoin concentration and absorbance. This confirms that the method is suitable and reliable for analysing the drug.

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Standard Curve in Distilled Water

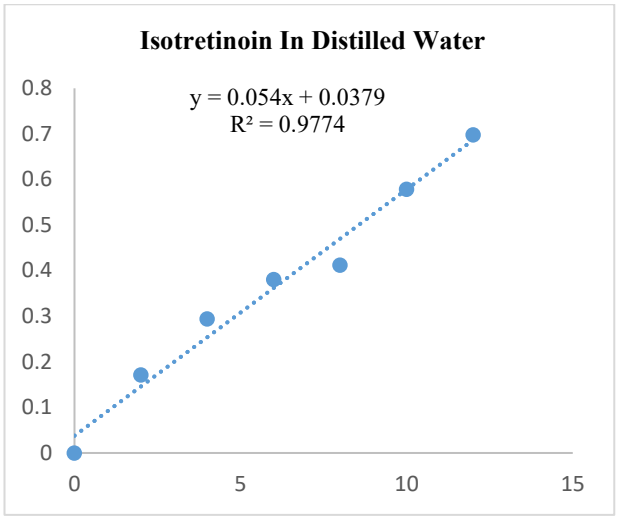


Table no.3

Conc.	Abs
0	0
2	0.171
4	0.274
6	0.38
8	0.412
10	0.577
12	0.699

Fig No.8

Standard Curve of Isotretinoin in 0.1 N HCL (pH 1.2)

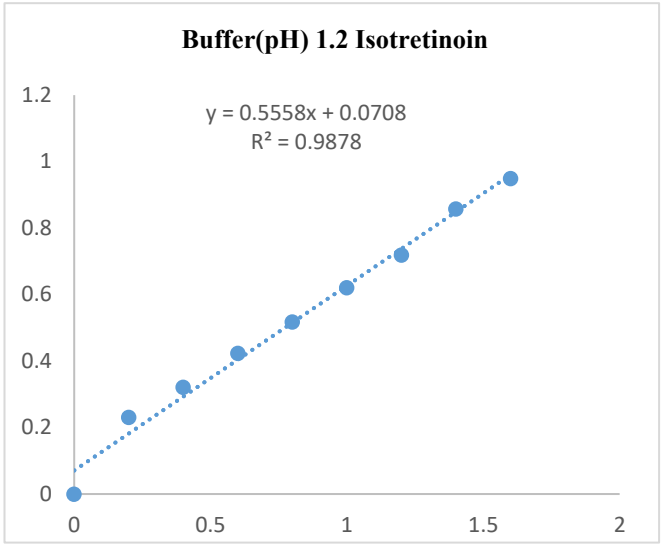
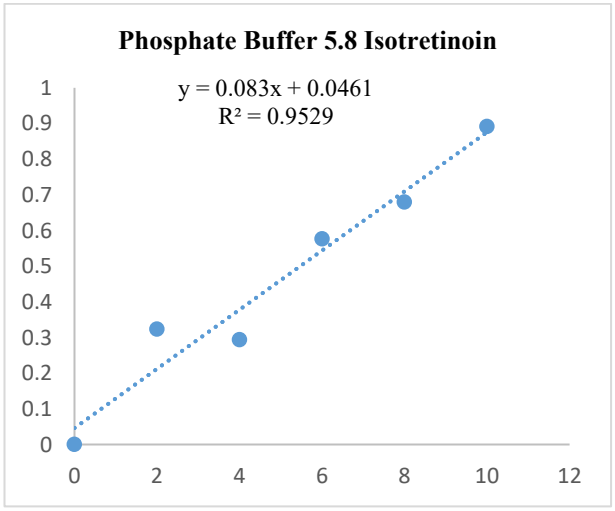


Table no. 4

Conc.	Abs
0	0
0.2	0.231
0.4	0.322
0.6	0.424
0.8	0.517
1	0.62
1.2	0.718
1.4	0.857
1.6	0.949

(pH 5.8)

Table no.5

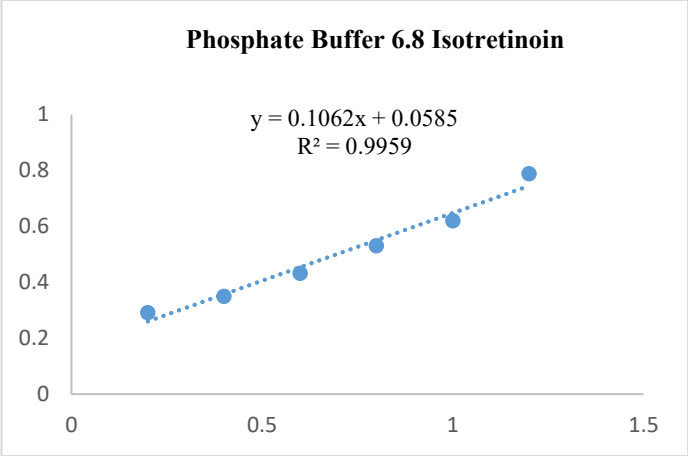


Conc.	Abs
0	0
0.2	0.326
0.4	0.468
0.6	0.577
0.8	0.679
1	0.888

Fig No.10

Standard Curve of Isotretinoin in Phosphate Buffer (pH 6.8)

Table no.6

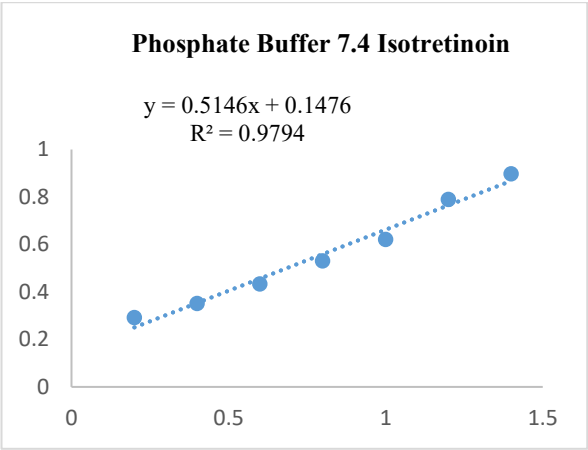


Conc	Abs
0	0
0.2	0.181
0.4	0.261
0.6	0.37
0.8	0.478
1	0.579
1.2	0.712

Fig No.11

Standard Curve of Isotretinoin in Phosphate Buffer (pH 7.4)

Table no.7



Conc	Abs
0	0
0.2	0.292
0.4	0.351
0.6	0.433
0.8	0.531
1	0.621
1.2	0.789

Fig No.12

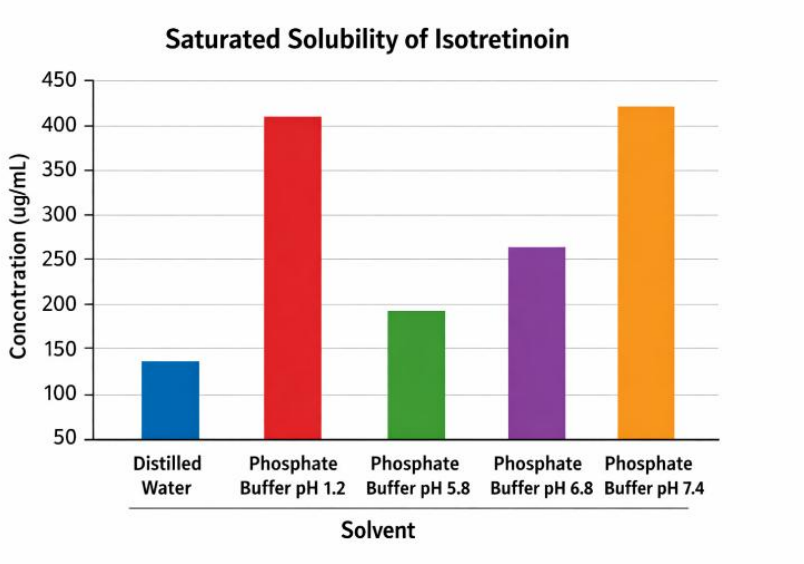
Table no.7

Sr. No.	Solvent Used for Study	Linear Equation (y = mx + c)	Correlation Coefficient (r^2)
1	Distilled Water	y = 0.054x + 0.0379	0.9774
2	0.1 N HCL pH 1.2	y = 0.5558x + 0.0708	0.9878
2	Phosphate Buffer pH 5.8	y = 0.083x + 0.0461	0.9529
3	Phosphate Buffer pH 6.8	y = 0.1062x + 0.0585	0.9959
4	Phosphate Buffer pH 7.4	y = 0.5146x + 0.1476	0.9794

Saturated Solubility Study of Isotretinoin

The results of the saturated solubility study are shown in Fig. 11. The data indicate that the solubility of Isotretinoin is pH-dependent, with solubility increasing as the pH of the medium increases. The drug showed the lowest solubility in distilled water, which may be due to its predominantly unionized form in this medium. While the unionized form Favors membrane permeability, it reduces the overall solubility of the drug.

Fig No.10



Conclusion:

The study of isotretinoin solubility and UV–Visible spectroscopy in various dissolution media demonstrated that the drug's solubility depends on the pH of the medium. The maximum absorption wavelength (λmax) remained almost unchanged across all tested media, suggesting that the drug's light absorption properties are not significantly affected by pH. Calibration curves constructed in distilled water and buffer solutions (pH 1.2, 5.8, 6.8, and 7.4) showed excellent linearity, confirming that UV–Visible spectroscopy is a reliable method for determining isotretinoin concentrations.

Saturated solubility tests indicated that isotretinoin is least soluble in distilled water, with solubility increasing as the pH rises. This pattern is likely due to the predominance of the unionized form in acidic and neutral conditions, which enhances membrane permeability but reduces solubility in aqueous solutions. These results emphasize the need to account for pH and ionization when designing oral formulations of isotretinoin to improve its bioavailability, consistent with its BCS Class II classification (low solubility, high permeability).

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